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PATHOLOGIC AND IMMUNOLOGIC PROBLEMS IN THE VIRUS FIELD. By THOMAS M. RIVERS, M.D. 435

THE SEROLOGIC CLASSIFICATION OF HEMOLYTIC STREPTOCOCCI IN RELATION TO EPIDEMIOLOGIC PROBLEMS. By HOMER F. SWIFT, M.D., REBECCA C. LANCEFIELD, PH.D., and KENNETH GOODNER, PH.D. 445

ACUTE VASOSPASTIC HYPERTENSION. A CASE WITH SIGNS OF CEREBRAL IRRITATION AND SEVERE RETINITIS WITH REMISSION. By NORMAN M. KEITH, M.D., and HENRY P. WAGENER, M.D. 454

A SUGGESTION FOR SIMPLE TREATMENT OF ACUTE ARTERIAL SPASM. By EDWIN P. LEHMAN, M.D. 459

A STUDY OF THE VENOUS BLOOD PRESSURE IN SOME COMMON DISEASES. By WILLIAM B. WARTMAN, M.D. 464

THE DEMONSTRATION OF COLLATERAL VENOUS CIRCULATION IN THE ABDOMINAL WALL BY MEANS OF INFRA-RED PHOTOGRAPHY. By EDGAR JONES, M.D. . 478

STUDIES OF PERIPHERAL VASCULAR PHENOMENA. IV. THE EFFECT OF ARTIFICIAL FEVER ON THE PULSE VOLUME CHANGES OF THE FINGER. By CARL A. JOHNSON, M.D., STAFFORD OSBORNE, B.P.E., and GEORGE SCUPHAM, M.D. . . . 485

METABOLIC RATES IN THERAPEUTIC FEVER. By ISRAEL KOPP, M.D. 491

A STUDY OF THE COAGULATION DEFECT IN HEMOPHILIA AND IN JAUNDICE. By ARMAND J. QUICK, PH.D., M.D., MARGARET STANLEY-BROWN, M.D., and FREDERIC W. BANCROFT, M.D. 501

GAUCHER'S DISEASE OF LATE ONSET WITH KIDNEY INVOLVEMENT AND HUGE SPLEEN. By JOHN S. HORSLEY, JR., M.D., JAMES P. BAKER, JR., B.A., M.D., and FRANK L. APPERLY, M.A., M.D., D.Sc. 511

HYPERPARATHYROIDISM WITH RENAL INSUFFICIENCY. By DAVID E. BELLIN, M.A., M.D., and BENJAMIN S. GERSHWIN, M.D. 519

PELLAGRA. AN ANALYSIS OF CASES ADMITTED TO THE PENNSYLVANIA HOSPITAL SINCE 1922. By THOMAS C. GARRETT, M.D. 525

THE PSYCHOLOGIC BACKGROUND OF COLITIS. By FRANK BODMAN, M.D. . . 535

THE COMMON DENOMINATOR OF DISEASE. By GEORGE DRAPER, M.D. . . . 545

INDEX TO PHYSICIAN'S SUPPLIES . . . . . ADV. PAGE 38

Contents continued on adv. page 10

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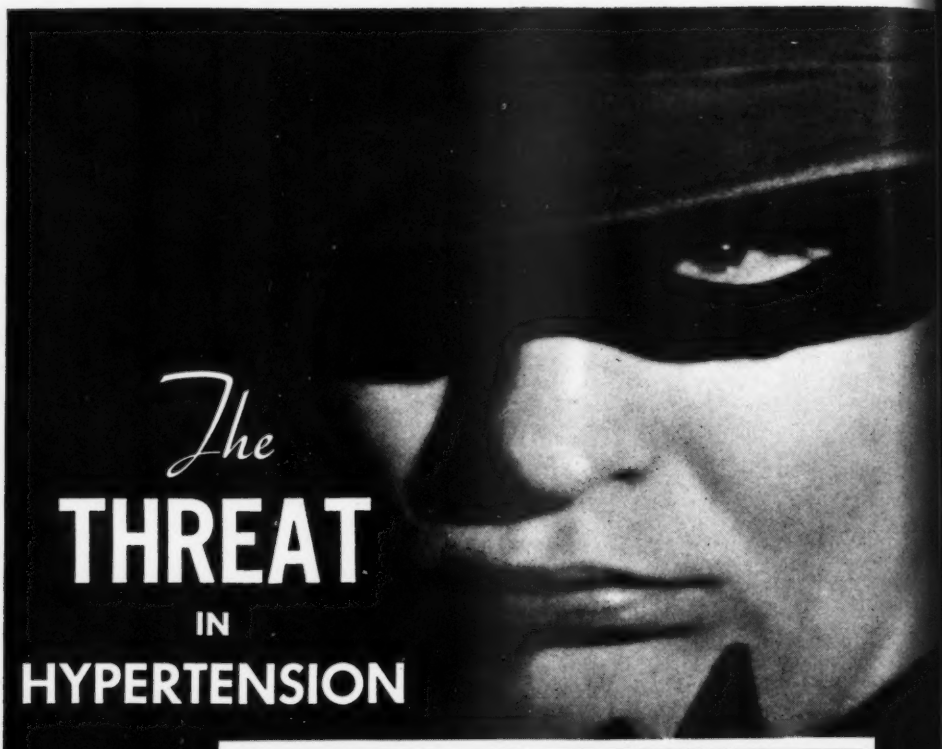

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

OCTOBER, 1935

ORIGINAL ARTICLES.

PATHOLOGIC AND IMMUNOLOGIC PROBLEMS IN THE VIRUS FIELD.*

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(From the Hospital of The Rockefeller Institute.)

The nature of this symposium requires discussion of both pathologic and immunologic phenomena associated with virus diseases. I shall also call attention to certain problems undergoing or awaiting solution in this field.

Viruses or filterable viruses were first shown to exist and are still principally recognized clinically and experimentally by means of their activity in a host. Therefore, I shall begin this talk by describing certain pathologic phenomena and discussing their significance.

When the pathology of virus diseases is mentioned, it is customary for the question of inclusion bodies to arise immediately. These bodies are not necessarily the most significant feature of the pathologic changes seen in tissues affected by viruses. Nevertheless, it seems advisable to dispose of them before going to phenomena of greater significance.

In many, but not all virus diseases, significant intracellular changes spoken of as inclusion bodies have been described. Some of the changes were recognized many years ago; Paterson, for instance, described molluscum corpuscles in 1841.

Most workers now admit that inclusion bodies are significant and

* Presented before a joint meeting of the American Association of Pathologists and Bacteriologists and the American Association of Immunologists, New York City, April 18, 1935.

rarely exist in the absence of the activity of a virus. The nature of all of these bodies is not known. For example, the nuclear inclusions found in herpes febrilis, herpes zoster, varicella, Virus III infections in rabbits, yellow fever, guinea pig salivary gland disease, equine encephalomyelitis, pseudorabies, and B virus disease, are still a source of differences of opinion. On the other hand, within recent years there has been a certain amount of crystallization of opinion in regard to some of the cytoplasmic inclusions.

In 1873, Bollinger found large cytoplasmic inclusions in cells infected with fowl pox virus, and, in 1892, Guarnieri found similar inclusions in the cytoplasm of cells affected by vaccinia. In 1904, Borrel observed minute coccoid bodies in smears made from fowl pox lesions. Similar bodies were observed in 1906 by Paschen in smears of material from vaccinal lesions. For a long time many workers either denied the existence of all these bodies or failed to grasp their significance. The recent work of Goodpasture,[1] Ledingham,[2] Craigie,[3] and others, however, has clearly established the fact that these minute bodies, approximately 150 to 175mμ in diameter and invisible by means of ordinary light, either represent the viruses of fowl pox and vaccinia or are intimately associated with the active agents inciting the diseases. Furthermore, it appears that the Bollinger and Guarnieri bodies are composed chiefly of aggregates of the minute coccoid structures.

The minute forms under discussion are usually spoken of as elementary bodies and play an important rôle in diseases other than fowl pox and vaccinia,[1] for example infectious ectromelia of mice, psittacosis, smallpox, canary pox and probably other pock maladies. The exact nature of elementary bodies is not known. Nevertheless, they have played an important part in recent immunologic and serologic studies of vaccinia.

Minute structures similar to elementary bodies have been described as occurring in smears containing the active agents of foot-and-mouth disease and bacteriophagy. Much doubt naturally exists in regard to the importance of such structures, because the active agents of these diseases (foot-and-mouth disease virus being 8 to 12mμ in diameter) are so small that it is hardly conceivable that they can be made visible by mordants and stains. Moreover, it is wise to suspend judgment of Ledingham and Gye's[4] recent report on elementary bodies in association with the viruses causing filterable tumors in chickens.

Viruses seem to be obligate parasites, requiring an association with susceptible cells for multiplication. Consequently, it is not unreasonable to suppose that their relation to host cells and the reaction of these to their presence and activity should result in phenomena of importance and significance. In the case of certain viruses, inclusion bodies represent one of the phenomena resulting from such an association. Although the inclusion bodies have

attracted a great deal of attention in the past and have caused an untold amount of discussion, I believe that there are certain reactions of tissues to viruses, so obvious that they are ignored, which are of more fundamental importance than are the inclusion bodies themselves. I refer to proliferation, proliferation followed by necrosis, and necrosis, changes which give to the lesions their pathognomonic characters. In 1928, I[5] wrote at length concerning these reactions and since that time other workers, *e. g.*, Goodpasture,[6] Shope,[7] Andrewes[8] and Rous and Beard[9] have expressed opinions about the matter. In view of the fact that many virus diseases are acute infections, one doubtless wonders what part I consider inflammation to play in the pathologic pictures. Inflammation in virus maladies is a secondary phenomenon while hyperplasia and necrosis of the affected cells are the primary, most important, and most characteristic reactions of cells to this type of infection.

The following brief description seems to portray with a reasonable amount of accuracy what actually occurs when viruses attack their hosts. These highly parasitic agents multiply on or in susceptible cells and cause symptoms and signs of disease only when they come in contact with such cells. If the action of the viruses is not extremely rapid and explosive, and if the susceptible cells are capable of multiplication, the primary effect of the active agents is stimulation leading to cellular hyperplasia. Following the hyperplasia there is usually a destruction or necrosis of the cells which in turn is attended or followed by a secondary inflammation representing the reaction of the neighboring tissues and of the host. The balance between the stimulative and destructive tendencies of the viruses determines whether hyperplasia or necrosis is the predominant part of the pathologic picture. Thus, in some virus diseases, for example, vaccinia, varicella, smallpox, and fever blisters, vesicles (*i. e.*, necrosis) occur; in others, *e. g.*, warts and tumors, an overgrowth of tissue is the predominant feature. When vaccinia, smallpox, and fowl pox are mentioned, one usually visualizes vesicles and pustules. Nevertheless, in these maladies a hyperplasia of cells precedes the formation of vesicles. This fact is beautifully illustrated by sections prepared at the proper time from young fowl pox lesions or from rabbit corneas infected with vaccine virus or the virus of smallpox. If the action of the viruses is explosive or rapid, as for instance in yellow fever and Rift Valley fever, or if the susceptible cells are incapable of division and multiplication, as is the case with nerve cells, then the primary pathologic changes are necrobiosis and lysis of cells. The destruction of Purkinje cells[10] in the cerebellum of a monkey with louping ill is a striking example of the lysis of cells by viruses.

From what has been said it is obvious that viruses will enter into any discussion of the etiology of tumors and malignant growths. If one resists the temptation to split hairs, one must admit that

some tumors are caused by viruses. If one desires to split hairs, however, one can say that Rous' sarcomata and Shope's papilloma do not represent tumors but examples of virus hyperplasia. Regardless of what these disease processes are called, they still exist and must be recognized.

Granted that viruses produce growths having the characters of tumors, one is faced with the question, do viruses produce all tumors? Of course such a question cannot be answered at the present time. My guess is—and everyone working with viruses and tumors is entitled to a guess—my guess, then, is that tumors may arise as the result of more than one mechanism. Though Rous and Beard[11] have shown that the Shope papilloma has the immediate traits of a tumor and that in many instances this tumor undergoes malignant changes occurring in carcinomas, yet the facts are still open to several interpretations: 1, Both the benign papilloma and the malignant growth that sometimes supervenes after months may be caused by the same virus, a conditioning of the host cells having taken place in certain instances that permits an altered or malignant type of reaction to the virus instead of the papillomatous one that usually occurs. 2, The virus ordinarily producing the papilloma may undergo a change itself that enables it to cause a malignant growth instead of a benign papilloma. 3, The papilloma and the intercurrent bacterial infection that frequently accompanies many of the lesions may act as excellent highly specialized chronic irritants and as such induce malignant changes in the cells of the rabbit in a manner similar to that of repeated applications of tar to the skin. Interpretations one and two emphasize the presence and activity of a virus. On either assumption the malignant process would regress and disappear if the virus were removed from the body. In the third interpretation emphasis is placed on some change that occurs in the cells and is reflected in or inherited by daughter cells. Therefore, once such a change has occurred in the cells, the removal of the virus from the body would not influence the progress of the malignant growth any more than does a cessation of tarring lead to a cure of the malignant growth resulting from it.

At the moment it would be futile to pursue this matter further. Nevertheless, hyperplasia and necrosis are such important phenomena in the pathologic pictures produced by viruses that pertinent remarks had to be made concerning them if for no other reason than to show that such disease processes as tumors, warts, measles, fever blisters, smallpox, poliomyelitis, and bacteriophagy possess characteristic pathologic pictures in common in spite of the fact that they exhibit striking clinical differences.

Now we shall consider for a moment certain interesting immunologic problems encountered in the virus field. The active agents under discussion are undoubtedly antigenic, and, because of this fact, they should be of interest to immunologists. It has been shown

that agglutinins, precipitins, complement-fixing antibodies and neutralizing or protective antibodies may appear in the sera of individuals who have recovered from certain virus diseases. Moreover, an obvious infection with a virus usually leads to a state of increased resistance in the recovered host to further molestation by the same agent. It is of no particular interest, however, that such things take place in virus diseases, because they are known to occur in other types of infection. Nevertheless, there are some facts of particular interest which deserve consideration at this time. 1, Why is it so difficult to obtain an efficient immunity against virus infections by means of injections of vaccines composed of inactivated viruses? 2, Are the agglutinins, precipitins, complement-fixing antibodies, and protective antibodies the result of the stimulation of a host by means of a single antigen? If not, do the different antigens represent different fractions of the virus, or do some of the antigens arise in the host as a result of infection? 3, In what manner do the neutralizing or protective antibodies act? 4, Finally, why do so many virus diseases lead to a permanent immunity in recovered hosts?

Questions arising in regard to the immunization of individuals with inactive viruses are difficult to answer, because it is almost impossible at present to determine when a virus has been completely inactivated. For example, Lippert[12] doubts whether Perdrau and Todd by means of methylene blue and light completely inactivated the canine distemper virus which later was shown to immunize dogs against distemper. Further, Dunkin and Laidlaw have shown that formolized canine distemper virus will produce a fleeting immunity in vaccinated dogs, but in order to get a solid lasting resistance active virus must be employed. Certain workers are of the opinion that the amount of inactive virus is the all important factor *i. e.*, if a sufficient amount were used, a solid immunity would result. Mackenzie[13] reported that with small doses of inactive Rift Valley fever virus he was unable to immunize mice, while with large doses, 1 cc. administered intraperitoneally, he was able to establish a good resistance in the animals to the active agent. Assuming that the virus was completely inactivated and that the mice were solidly protected, one must remember that a mouse weighs in the neighborhood of 20 gm. and that 1 cc. or 1 gm. of the virus emulsion was administered, *i. e.*, approximately $\frac{1}{20}$ of the body weight. On the basis of these figures a man weighing 150 pounds would require $7\frac{1}{2}$ pounds of vaccine—not a very practical procedure. When one brings up the question of the production of immunity by an inactive virus, antirabic vaccination is cited as an example of protection induced in this manner. I am glad to find, however, that some workers, for example Webster and Dawson,[14] are no longer willing to accept dogmatic statements handed down to them in regard to antirabic vaccination, but insist upon exploring the field for themselves.

Whatever viruses may be, in an active state they are antigens, and as such one would like to think of them as containing proteins, or at least as being linked in some way to proteins. Therefore, if sufficient amounts of these agents in an inactive state, yet with their antigenic components not altered by inactivation, were administered to subjects in the form of vaccines, I would not be surprised to find complement-fixing antibodies, etc., appearing in the sera of vaccinated individuals, nor would I be disturbed to find that a certain amount of resistance to infection had resulted. In the past, however, it has not been possible to obtain viruses in sufficient amounts in a relatively pure state to determine what happens to their antigenic components when inactivated. Recently, Craigie[3,15] has opened up this field in regard to vaccinia and has found that vaccine virus is composed of several antigens some of which are extremely labile and appear to function in the production of resistance, while others are stable and induce the formation of agglutinins, etc. Parker,[16] working in my laboratory, has confirmed many of Craigie's findings. What Craigie has accomplished for vaccinia must be done with other maladies, and, in the meantime, generalizations should be suspended.

For the sake of argument let us assume that it has been demonstrated that a certain degree of immunity can be obtained by completely inactive virus, provided sufficient amounts are administered. What about the duration of the protection induced in this manner? All the evidence at hand seems to indicate that whatever protection is produced in this way endures only for a relatively short time. Strange to say, many workers do not seem to be disturbed by this fact. In the case of hogs and cattle that are raised for the meat market and will live for a short time only, it is not necessary to produce a lasting immunity. Nevertheless, the duration of an immunity produced by vaccines, particularly when the vaccines are expensive to make and difficult to administer, is of great importance in the protection of human beings against smallpox, yellow fever, measles, poliomyelitis, etc.

As I have already indicated, some of the viruses at least are probably made up of several antigenic components which function differently in the process of immunity. Now we would like to know whether all the antigens active in virus diseases are found in the viruses themselves. Several workers have raised this question, and Hughes[17] has brought some evidence to show that the precipitinogen found in the blood and tissues infected with yellow fever virus is not a part of the virus but arises in the host as a result of the infection. Furthermore, in view of the fact that it is difficult, and according to some workers impossible to demonstrate a union between certain viruses and their neutralizing antibodies, Sabin[18] has suggested that the antigens causing the production of neutralizing antibodies do not exist in the viruses but arise from the infected

host. This idea while interesting has as yet no definite experimental confirmation.

An appropriate amount of serum from a host recovered from a virus disease mixed with the homologous virus usually results in what is called a neutral mixture, *i. e.*, the mixture of virus and convalescent serum does not produce evidences of disease in a susceptible host. Because of this phenomenon workers have developed the habit of speaking of the virucidal action of convalescent serum. From the remarks that follow it will become obvious that "virucidal" is not the proper word to use in this connection.

Bedson,[19] Todd,[20] Andrewes,[21] Sabin[22] and others have shown by means of dilution, filtration, and ultracentrifugation that the viruses in the neutral mixtures spoken of above are not killed or inactivated. In fact, an abundance of active virus has been recovered from such mixtures. Moreover, certain investigators contend that contact of the viruses with immune sera *in vitro* for a number of days does not result either in their inactivation or in a union of them with the neutralizing or protective antibodies. Other workers, however, are of the opinion that union and inactivation finally occur under such circumstances.[19,23,24]

In spite of the fact that the question regarding the final union *in vitro* of viruses with the protective antibodies has not been settled, most workers are agreed that the viruses in the so-called neutral mixtures which are usually injected into animals shortly after preparation are not really dead or inactive. Further evidence in regard to this matter is obtained from Green's[25] *in vivo* experiments on fox encephalitis in which he found that most foxes receiving neutral mixtures do not become sick, but that in a certain percentage of the animals a typical disease occurs after a very long incubation period. A similar state of affairs has also been noted in work on poliomyelitis and has been interpreted as an indication that the virus in the neutral mixtures is not killed or inactivated, but is only held at bay for a time by the immune serum.

The facts related above are interesting, and one naturally desires to know why the mixtures of convalescent sera and viruses do not usually produce disease even though the viruses are still active. Several years ago we[26] attempted to throw light on the subject by the investigation of some of the phenomena in tissue cultures. As a result of this work we were able to show that typical vaccinal lesions developed in tissues that were exposed to vaccine virus for a short time and then cultivated in potent antivaccinal plasma. Furthermore, active vaccine virus was demonstrated in these cultures in spite of the immune plasma. In other words, immune plasma and normal cells did not inactivate vaccine virus. We went still further and showed that vaccine virus was not inactivated in cultures composed of immune cells, immune plasma, and virus.

Simultaneously with us, Andrewes[27] working with Virus III and herpes virus, and more recently Downie and McGaughey[28] working with infectious ectromelia, and Sabin[18] working with pseudorabies, herpes virus, and B virus have obtained similar if not identical results.

The facts that some viruses are not inactivated or killed either by mixtures of normal cells and immune serum or plasma or by mixture of immune cells and immune plasma or serum, are substantiated by the *in vivo* experiments of Tulloch[29] and Downie.[28] The former injected vaccine virus into the testicle of a passively immunized rabbit. No evidence of infection occurred, but 7 days later active vaccine virus was recovered from the normal-looking organ. The latter worker injected the virus of infectious ectromelia into an actively immune mouse and recovered active virus from the serum of the animal several days later.

From what has been said it is obvious that the manner in which the protective or neutralizing antibodies act is not definitely known. It is also evident that this is a very attractive field for further investigations.

It is well recognized that recovery from a virus infection is usually followed by an enduring immunity. In many instances the immunity is operative during the remainder of an individual's life. Of course there are exceptions to the rule. For example, common colds recur repeatedly in the same individual, and herpes simplex or fever blisters occur at frequent intervals in the same subjects. The persistence of immunity in hosts recovered from virus diseases is so striking that it is not surprising that an explanation of the phenomenon has been sought. Furthermore, if it is the rule to encounter a lasting immunity in virus diseases, one would like to know the reason for the exceptions.

In the case of poliomyelitis and measles, the viruses of which one encounters from time to time throughout life, one might explain the persistent immunity and the presence of neutralizing antibodies on the basis of repeated contacts with the active agents. On the other hand, it is impossible to explain in such a manner the enduring immunity to yellow fever, which is accompanied by the presence of humoral antibodies, in individuals who have been out of yellow fever zones for periods of 25 to 50 years.

In view of the facts mentioned above, and because it is known that a refractory state to some bacterial and spirochetal diseases is associated with a persistence of these agents in the hosts, it has been suggested by a number of workers that at least in certain instances the protracted immunity following virus diseases is due to a prolonged or a persistent sojourn of the viruses in hosts once infected. This persistence of the viruses does not indicate that the hosts are capable of spreading disease.

Before proceeding, it is necessary for me to cite a few instances

in which it has been definitely established that viruses persist in immune subjects. Once a guinea pig is infected with the salivary gland disease virus[30] it becomes immune and retains its immunity, yet the active agent can be recovered at any time from its salivary gland. Dr. Pearce and I[31] showed that Virus III is regularly carried by the Brown-Pearce carcinoma of rabbits and that rabbits inoculated with the tumor become immune to Virus III and exhibit neutralizing antibodies in their sera within 2 weeks after inoculation. Nevertheless, we were able to recover Virus III from metastases of the tumor removed several months after the animals had become immune to the virus. We also showed that vaccine virus persisted in the tumor for at least 2 months in spite of the fact that the rabbits harboring the new growth were refractory to the virus and possessed protective antibodies in their sera. The Rous virus is readily obtainable from tumors removed from chickens possessing humoral antibodies. Dr. Berry and I[32] demonstrated the virus of psittacosis in a parrot that had had no contact with other birds for a period of 18 months. Furthermore, this bird was the source of virus that caused the death of a human being. Meyer and Eddie[33] have shown that psittacosis virus persists for a long time in immune mice that have recovered from the disease. The virus of laryngotracheitis[34] can be recovered from immune birds. Theiler[35] working with an encephalomyelitis that occurs naturally in mice has been able to obtain the virus from the cords of mice 1 year after the animals have recovered from the disease. In this connection the findings of Price recorded by Kunkel[36] regarding ring spot in tobacco are pertinent. When plants are inoculated with the virus they suffer an acute attack of the disease. "A systemic form of infection follows the development of primary lesions. Plants regularly recover and are then immune. They never suffer a second attack. The virus is retained by and recoverable from all plants which have had the disease."

Sufficient examples have been cited to show that viruses can and do persist in immune hosts. Moreover, failure to recover them from immune hosts is not necessarily positive evidence that they are not present.

In what way is it possible for viruses to persist in an immune host? It is most likely that these agents are intracellular parasites, and as long as they remain situated within living cells are in no danger of being eliminated from the body. If they do not kill the host cells, they can multiply and pass into daughter host cells. In this manner it is possible for them to remain indefinitely in an immune host. Such is undoubtedly what happens in the case of the Rous tumor.

At this point it is well to speak of the apparent lack of a lasting immunity to fever blisters. This disease is particularly interesting because the individuals who have recurring attacks possess an

abundance of neutralizing antibodies in their sera. The paradox has been explained on the basis of the persistence of the virus in the cells of immune individuals who develop crops of blisters whenever subjected to the conditions that are encountered as the result of typhoid vaccination, common colds, and exposures to high temperatures for several hours, etc.

Why does one fail to develop a permanent immunity to common colds? I do not know. It is interesting to speculate, however. The cold virus may be unable to establish itself permanently in the host, it may act in a manner similar to that of fever blister virus, or the superficial nature of the infection caused by it may have something to do with the poor development of immunity. In connection with the last possibility, investigators should become familiar with Tyzzer's[37] work on coccidiosis in gallinaceous birds.

In conclusion, it can be stated that there is no definite reason as yet to believe that the general principles of immunity, many of which are not known or understood, fail to operate in the virus field. Most of the immunologic and serologic oddities encountered in this domain apparently can be accounted for either by the intimate type of parasitism exhibited by the viruses or by the multiplicity and lability of antigens involved.

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(Titles have been omitted for sake of brevity.)

THE SEROLOGIC CLASSIFICATION OF HEMOLYTIC STREPTOCOCCI IN RELATION TO EPIDEMIOLOGIC PROBLEMS.*

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and

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The object of this communication is to demonstrate the application of recently perfected serologic methods in the epidemiologic study of Strep. hæmolyticus infections in limited populations.

Much of the earlier work on the subclassification of Strep. hæmolyticus was directed toward the establishment of specific pathogenicity. Thus many workers sought to establish differential characteristics which would enable them to distinguish between strains believed to be the specific etiologic agents involved in various diseases. For example, at one time it was thought that certain strains of Strep. hæmolyticus were specifically responsible for erysipelas, others for scarlet fever and that still others caused septic sore throat. This conception was the natural development of findings in the typhoid-parathyphoid group of bacteria where specific pathogenesis could generally be correlated with biochemical and serologic characteristics of the microörganisms.

No satisfactory classification of the hemolytic streptococci on this basis has as yet been proposed. Indeed, it is evident from many recent studies that any one of these infections, although a characteristic clinical entity, may be associated in different individuals with entirely distinct strains of Strep. hæmolyticus. Similarly, it has been amply demonstrated that the same strain may in different

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patients be associated with entirely different clinical manifestations, ranging from generalized infections on the one hand to simple pharyngitis on the other.

Lancefield[1] has shown that hemolytic streptococci can be differentiated serologically by means of the precipitin reaction into distinct and sharply defined groups. The method is relatively simple and gives results which are strikingly uniform and constant. It is based on the fact that the strains of each group contain a common specific carbohydrate, the so-called "C" substance. These groups, designated by the letters "A," "B," "C," etc., are shown in Table 1, together with the information now available as to the natural habitats of the members of these groups.

TABLE 1.—CURRENTLY IDENTIFIED SEROLOGIC GROUPS OF HEMOLYTIC STREPTOCOCCI.[1,5]

Group.	Probable normal habitat.	Probable secondary habitats.	
		Associated with infections.	Not associated with infections.
A . . .	Human carriers Human infections: Scarlet fever. Puerperal sepsis. Erysipelas. Septic sore throat. Pneumonia, etc.	Cattle: mastitis. Laboratory animals.	
B . . .	Cattle: mastitis. Milk.		Human throat and vagina.
C . . .	Horses: strangles. endometritis. Cattle: mastitis. Guinea pigs: adenitis. Also in infections of many other animals, as rabbits, foxes, swine, fowls.		Human throat and vagina.
D . . .	Cheese.		Human throat, intestine and vagina.
E . . .	Milk.		
F . . .	Man: respiratory tract.		
G . . .	Man: respiratory tract. Monkey: normal throat. pneumonia. Dog: otitis.		

Group A comprises most hemolytic streptococci which have been isolated from human infections and also includes a large number of strains isolated from human carriers. Representatives of this group have occasionally been isolated from infections in lower animals.

The most notable instance of this finding is in bovine mastitis, occurring secondarily to an infection of the milker or other attendant; and this type of mastitis has been the source, at times, of milk-borne epidemics of septic sore throat or of scarlet fever. Small animals in the laboratory have occasionally been found to be infected with Group A streptococci. Many of these animals, on the other hand, are susceptible to inoculation with Group A strains, when they are introduced parenterally.

The large majority of disease-inducing strains in domestic and wild animals have, on the other hand, been found to belong to Groups B and C; and these, in turn, appear to have little spontaneous pathogenicity for human beings, even though they be harbored in the throat, intestine or vagina. Mastitis in cattle, while most commonly induced by members of Group B or C,[2,3] may, as above noted, be caused by members of Group A. Groups D and E, found in dairy products, and hence probably coming from cattle, have not been shown to have pathogenicity for any animal. Thus, while any of these five groups may occur in milk or dairy products, only members of Group A have any marked potential pathogenicity for man. When, therefore, members of this group are found in milk the inference to be drawn is either that the cows furnishing the milk have mastitis due to a Group A streptococcus, or that the milk has become contaminated from a sick man or from a human carrier. It seems probable, therefore, that any milk in which Group A hemolytic streptococci are found is unfit for human consumption unless pasteurized. Probably the presence of strains other than Group A in the throat, intestine or vagina of human beings arises from the consumption of milk or other food products containing them.

More detailed discussion of the specific disease-inducing capacities of Group B and C strains for lower animals would lead us too far afield; but we can state that most epidemics of streptococcal diseases among domestic and laboratory animals are caused by these groups. Possibly the disappointing results—insofar as obtaining exact parallelism between human diseases and infections in artificially inoculated lower animals is concerned—are due to the differing susceptibility of different mammalian species to different groups of streptococci. Somewhat comparable conditions exist in the case of tubercle bacilli: bovine and avian strains have much different disease-inducing capacities for man than for cattle or birds. It is to be hoped that some laboratory animal may eventually be found which will lend itself to study of Group A streptococcal infections in much the same manner as guinea pigs inoculated with human tubercle bacilli have tuberculosis comparable to that of man.

The pathogenicity of Groups F and G is little understood; but at present Long and Bliss[4] are actively investigating this question in respect of Group F.

An excellent example of the application of the method of grouping is to be found in the recent work of Lancefield and Hare[5] on the serologic differentiation of pathogenic and non-pathogenic strains of hemolytic streptococci from parturient women. It was found that all strains causing puerperal infections were members of Group A, while of 96 strains isolated from patients with afebrile puerpera, only 1 belonged to Group A; the others were distributed through Groups B to G. Because most severe postpartum sepsis is the result of infection with streptococci from sources extraneous to the patient,[6] such as carriers, or from other patients with streptococcal infections, the method of grouping offers a technique for keeping these potential sources of danger from the patient at this very vulnerable period. Group A strains in the respiratory tract of the expectant mother may become very dangerous when transferred to her genital tract. Other groups of streptococci may, on the other hand, be carried by either mother or contacts with relative impunity. For this reason one of the points of attack in preventing puerperal sepsis would appear to be the immunological identification of streptococci in these individuals, and rigid exclusion of the carriers of Group A strains.

TABLE 2.—CURRENTLY IDENTIFIED SEROLOGIC TYPES OF HEMOLYTIC STREPTOCOCCI.

Group differentiation.	Group.	Type differentiation.
Differentiated into groups by specificity of carbohydrate "C"	A	Divided into serologic types on the basis of specificity of "M" substance (Lancefield[8]), or by slide agglutination (Griffith[10]).
	B	Divided into 4 or more types on the basis of specificity of polysaccharid "S" (Stableforth[3]), (Lancefield[17]).
	C	(Tentatively divided into 4 types on the basis of fermentation reactions) (Edwards[2]); serologic types not determined.
	D, E, F, G	Serologic types known to exist but differentiation still incomplete.
	Other groups known to exist but as yet incompletely studied.	

Grouping, however, is only the first step in the complete system of classification. The second requirement, particularly important for epidemiological studies, is the differentiation of types within each group. Dochez, Avery and Lancefield[7] originally observed that strains of hemolytic streptococci associated with infections in man lend themselves to typing in much the same way as do the

pneumococci. Although this finding and corroborative observations by many workers appeared before the development of knowledge of the groups, this fact now serves as the necessary complement to the complete system classification.

The current conception of hemolytic streptococcal *typing* is summarized in Table 2. The division into groups has already been described. For type differentiation in Group A, Lancefield[8] employs the precipitin test with acid extracts of the streptococci—the so-called M fraction—and suitably prepared immune rabbit sera. The results of this method have been shown to parallel those obtained with the specific agglutination and protection tests.[8,9] Griffith[10] advocates a special slide-agglutination technique with especially absorbed sera, and has described more than 20 types. Neither of these methods of typing is as yet sufficiently simple to permit of use by workers other than those skilled in immunologic technique.

It is unnecessary in the present paper to discuss in detail the problem of typing in the other groups of streptococci, although the principle of typing has distinct application in epidemics among lower animals.[2,3]

Two examples of the epidemiologic application of the system of grouping and typing of hemolytic streptococci may be cited. During March, 1933, 4 cases of streptococcal otitis media occurred among measles patients in an isolation ward made up of separate rooms. A nurse in contact with these patients also developed otitis media followed by mastoiditis. A kitchen helper on the ward developed streptococcal pharyngitis. During the next month there occurred among the patients on this ward 4 additional cases of otitis media, 2 of pharyngitis, and 1 child developed cervical abscess. All of these infections were associated with hemolytic streptococci. At various times during this period 3 nurses and 1 physician, not on duty on this ward, suffered from tonsillitis.

Strains of Strep. hæmolyticus recovered from this series of cases all proved to be members of Group A, but there was a considerable diversity of types. Two of the patients with otitis media, together with the nurse and the kitchen helper had been infected with one type, 3 of the patients with another type, 2 with a third. The remaining strains did not fall into any of the types for which differential sera were available. These studies made it evident that there had been at least four sources of infection.

During the past winter it was possible to study another institutional outbreak of streptococcus infections. This occurred in a ward made up of patients, mostly of children, suffering from nephrosis and nephritis. Within a period of 1 month, 7 of these patients suffered acute upper respiratory infections, with marked fever and signs of intoxication. Only 1 patient on the ward escaped infection. At the time of this outbreak 44 possible contacts among the hospital

personnel were shown not to be carrying hemolytic streptococci in their throats. At the same time, however, Nurse Fe., from another ward, was found to have a hemolytic streptococcal angina, and Nurse Ca., who was on duty on the ward involved, was found to be suffering from ethmoiditis of 3 weeks' duration. Swabbings from her nasal cavity at this time yielded almost pure cultures of Strep. hæmolyticus. Obviously, both nurses were possible sources of the

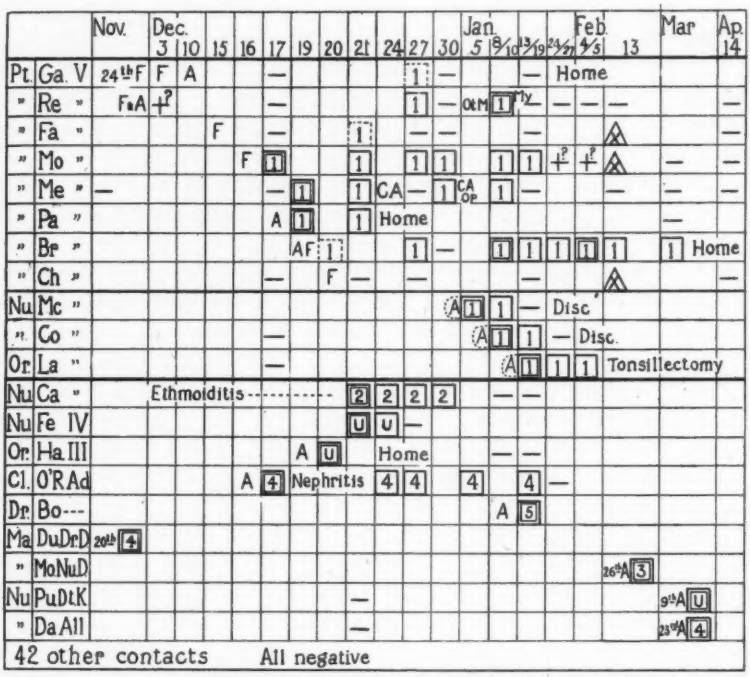

FIG. 1.—Summary of a hemolytic streptococcal epidemic in a ward and of other streptococcal infections among contacts. *F* indicates fever; *A*, angina; *Ot.M*, otitis media; *My*, myringotomy; *CA*, cervical adenitis; *OP*, cervical abscess incised. Solid squares indicate that the strain of streptococcus was identified. Dotted squares indicate that the strain of streptococcus was not identified, but was probably of the type designated. Numbers in squares indicate serologic type. U in squares indicate types not determined. — indicates cultures showed no hemolytic streptococci. $+^{?}$ indicates that hemolytic streptococci were recovered but not identified. Roman numerals indicate ward where patient was ill, or where nurses (Nu) or orderlies (Or) were on duty. Ma indicates maid in doctors' dining room (Dr. D), or nurses' dining room (Nu.D). Dt.K indicates diet kitchen. Ad indicates admission desk.

ward infection. Another possible source was a clerk, O'R., who was stationed at the office desk and who handled packages and mail that were sent to the ward. Simultaneously with the ward epidemic he developed a hemolytic streptococcal pharyngitis followed by hemorrhagic nephritis.

About 2 weeks after the original outbreak 2 nurses and an orderly on duty on this ward developed severe tonsillitis. As usual, during the winter months other members of the hospital personnel devel-

oped, within this general period, angina or tonsillitis from which hemolytic streptococci were recovered.

The strains of hemolytic streptococci isolated from these patients and contacts were subjected to the various tests for classification. The results of these studies, together with the information given above, but in a highly condensed form, are presented in Fig. 1. The numerals in the various squares indicate the respective types: "U" indicates that the strain isolated did not fall into any type for which serum was available. It should be pointed out that these type numbers have no relation to those employed by Griffith,[10] but are used in this particular study merely as a convenient means of designation.

From the data presented in Figure 1 it will be noted that the strains of hemolytic streptococci isolated from the patients involved in the epidemic were all of the same type. Likewise this type occurred with those three contact attendants who subsequently developed infections. On the other hand, strains from 9 other individuals, all possible contacts, either as sources of the original infection or as secondary cases, proved to be of entirely different types.

February 13, 3 of the patients had mild upper respiratory infections, and yielded cultures of hemolytic streptococci of entirely different colonial morphology from those previously observed. Further serologic study of these strains showed that they belonged to none of the groups for which sera were available. Their detection is indicated in the chart by a triangle.

From these studies it seems probable that none of the hospital personnel could have been the source of the strain which initiated the epidemic. It seems most likely that this was introduced into the ward by patient Re., who on admission was convalescing from an upper respiratory infection. Another possible source was from ward visitors, since it is well recognized that these persons often bring in infectious agents.

Dicussion. As a result of the work cited, it is obvious that hemolytic streptococci can be differentiated into a system of groups and types. It has been demonstrated that the types are as highly specific as are the types of pneumococci and, like these latter, are characterized by immunologically specific chemical components. A serologic system of classification offers a basis for the elimination of much of the confusion which has obscured the problem of hemolytic streptococcal infection. For instance, in England, Griffith[10] has worked for the last decade upon the question of typing hemolytic streptococci obtained from man by means of a slide-agglutination technique with broth cultures and specifically absorbed immune rabbit serum, and has found that most of the strains isolated in that country fall into 24 types. Four additional types described by him have subsequently been shown to belong in other groups of Lancefield's classification. The pathogenicity of these 4 types for

man had been questioned by Griffith; but their description among the strains commonly pathogenic for man illustrates the desirability of grouping streptococci before attempting to type them.

In collaboration with health and school officials, Griffith has been able to trace the course of many epidemics, and has shown that in institutions a primary epidemic wave was often due to one immunological type of streptococcus which, in turn, was followed by secondary waves due to the same type. In subsequent years other epidemics in the same institution were usually due to still other types. In some milk-borne epidemics Griffith found all of the patients were infected by a single type.

Some question has been raised as to whether the agglutination method employed by Griffith and the anti-M precipitin method devised by Lancefield will give absolutely parallel results in all of the types. Although this question cannot be definitely resolved until the two methods have been compared with all obtainable types, nevertheless where comparative tests have been applied with the same strains in this laboratory the two methods appear generally to agree.

Efforts have been instituted to achieve uniformity in designating groups and types in England and this country. If this most desirable goal can be attained, the methods of classification now available would permit of studies of epidemics on a much wider scale than has hitherto been possible. Sufficiently numerous data, gathered with a common viewpoint and with a uniform nomenclature, would eventually render it possible to compare other features of streptococcal infections with the types of microörganisms causing them. For example, Griffith[10] has found at least 15 different serologic types in cultures from patients with scarlet fever; and Williams,[11] Coburn and Pauli,[12] and others have demonstrated a similar diversity of types among the strains isolated from other so-called specific infections.

We do not desire to leave the impression that all of the problems of hemolytic streptococcal infections are to be solved simply with the technique of immunologic classification, for this is probably far from the case. Streptococci have many potentialities besides the elaboration of group and type specific antigens. Erythrogenic toxins,[13] hemolysins,[14] fibrinolysins,[15] leukocidins and other toxins, such as those described by Weld,[16] have been demonstrated in the media of cultures grown *in vitro*, and corresponding antibodies have been found in the sera of animals and men infected with streptococci. Under suitable conditions pyogenic functions are well marked. Certain types may have higher invasive properties than others, and hence have more marked potentialities for setting up epidemics. The same serologic type, moreover, may vary in its pathogenic capacities.

While many of the functions of streptococci are still undetermined, it is possible for clinicians and health officers to obtain a much better

understanding of some of the problems of hemolytic streptococcal infection by employing the techniques now at their disposal. The application of certain of them to epidemiologic studies have been illustrated in the examples presented in this communication; although, in view of the possibilities offered, these examples must be regarded as preliminary in nature.

Summary. Recently devised immunologic methods for classifying hemolytic streptococci into groups and types are reviewed; and illustrations are presented showing how the two categories are applicable to different situations. Grouping permits one to obtain an approximate idea of the animal species from which the strain originally arose, and of its potential pathogenicity for man. The group of hemolytic streptococci characteristically pathogenic for man (Group A) can be subdivided into serologic types; and from this typing the course of epidemics in limited populations can be accurately followed.

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ACUTE VASOSPASTIC HYPERTENSION.

A Case With Signs of Cerebral Irritation and Severe Retinitis With Remission.

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Two years ago a young woman who had been under observation at the clinic for many years, became afflicted within a few months by a severe form of diffuse arterial disease with hypertension. During the early acute phase of the condition her symptoms were severe headache, transient blindness, and hemianopsia. With the subsidence of these early visual disturbances there gradually developed a diffuse retinitis which in a few weeks became so extensive that there was edema of the optic discs and involvement of the macular regions. Vision was again impaired, and the woman was unable to read. After treatment in hospital, extending over a period of 1 month, her headaches became less severe and the retinitis began to subside. Slow recovery took place in the next 3 to 4 months. For 1 year there has been no active retinitis. During this last year, in spite of continued hypertension, the patient has been able to carry out about half of her household duties, and has been free from uncomfortable symptoms except for an occasional headache and tiring easily.

Case Report. The patient, a woman, now aged 31, first came to the clinic at the age of 11 and has thus been under our observation for 20 years. On her first admission she was in good health; the complaints were minor. In August, 1920, at the age of 17, she was found to have enlarged cervical nodes, presumably tuberculous. In 1921 infected tonsils were removed; examination of the urine gave negative results. She gave, for the first time, a history of migrainous headaches, which have persisted in varying intensity ever since. In 1922 she underwent a bilateral radical surgical operation for the suspected tuberculous glands, and histologic examination confirmed the diagnosis of tuberculous adenitis. In 1924 she had her first baby. Apparently there were no untoward events during pregnancy. In 1927 vision in her left eye became poor. In 1929 she had her second pregnancy, and apparently was in normal health. During the prenatal period she had very good care and was seen by Dr. Randall and Dr. Mussey. Delivery was in July, 1929. It is interesting to note that preceding and following the delivery the patient had no albuminuria or hypertension. In October, 1929, the ocular fundi were normal except for the presence of healed tuberculous chorioretinitis in the left macular region. In February, 1930, routine urinalysis gave results which were negative, as they always had been on previous visits. In March, 1932, the blood pressure was 110 mm. Hg systolic and 70 diastolic. Previous

to that date the records of blood pressure were also within the limits of normal. In August, 1932, she came in for refraction because of headaches. No lesion was found in the fundus except the old, central choroiditis of the left eye.

In November, 1932, because of increasing severity of headaches, she came for general physical examination. The systolic blood pressure was found to be 220 and the diastolic, 140. November 29, the arterioles of the fundi were markedly attenuated, especially the nasal branches in each eye, but there was no retinitis. She was put in the hospital for observation and remained there for 1 week. The patient appeared to be healthy. She did not appear anemic, and blood examination revealed normal hemoglobin and erythrocyte figures. Her blood pressure, which was 200 mm. Hg systolic and 130 diastolic, fell to 160 systolic and 90 diastolic. There was no demonstrable cardiac enlargement; the aortic second sound was moderately accentuated. The peripheral arteries on palpation were not definitely thickened, but gave to the examiner the sensation of a thickened rubber tube. The headache was the distressing symptom, together with attacks of vomiting. There was albumin, Grade 3, in the urine, but no red blood cells or casts. The values for blood urea and serum sulphate were normal, although urea clearance was reduced to 25 cc. of blood cleared per minute. Excretion of water was normal. While the woman was in hospital, one small hemorrhagic area appeared in the right retina (Table 1).

Two weeks later she was brought into the hospital in a stuporous, semiconscious, peculiar mental state. She complained that her vision had become suddenly blurred following several days of severe headache. At 7.30 A.M. she was apparently totally blind; at 9.30 A.M. she was able to perceive moving objects and had a left homonymous hemianopsia.

On *physical examination* gross abnormalities were not found. The blood pressure was 205 mm. systolic and 140 diastolic. Ophthalmoscopic examination revealed marked constriction of the retinal arteries, with considerable spastic irregularity. Several hemorrhagic areas and cotton wool patches were present in the right retina. Dr. Woltman thought the woman might have tuberculous meningitis. On lumbar puncture, the cerebrospinal fluid was under a pressure of 25 cm. of water, but the fluid was normal. Removal of 12 cc. of fluid did not relieve the headache. The next day, the visual fields were normal and the woman was able to read a newspaper. There was no actual paralysis. In the course of this visit, we gave her hypertonic solutions intravenously, with apparent benefit. These solutions included 20 to 25% solution of sucrose, either alone or combined with 3% solution of acacia. However, the retinal lesions increased during her stay in the hospital. Routine urinalysis disclosed albumin, Grade 1 to 3, but no erythrocytes or casts. Studies of renal function indicated a normal concentration of blood urea, slightly elevated serum sulphate, and reduced urea clearance (46 cc. of blood cleared per minute). A fortnight after the woman's dismissal from hospital her headaches still continued, so she reëntered the hospital and remained there for 4 weeks. During the 2 weeks at home her vision had failed so that she had been unable to read. Typical retinitis of so-called malignant hypertension had developed, with edema of the optic discs, numerous cotton-wool patches and hemorrhagic areas, and a partial macular star in the right eye. The arterioles were constricted to Grade 2 or 3 and the spastic irregularities were apparently developing into definite organic changes. Examination of arterioles of a small portion of the pectoralis major muscle, removed for histologic study, disclosed a decreased ratio of wall to lumen, 1.4, and a moderate increase in the intimal and medial nuclei. During this period, in January and February, 1933, we gave her repeated intravenous injections of hypertonic solutions of sucrose and glucose which also contained acacia. Deep

TABLE 1.—SUMMARY OF DATA ON THE CASE REPORTED.

Date.	Weight, kg.	Blood pressure.		Retina.				Blood.						Urine.						Comment.
		Systolic.	Diastolic.	Spasm, grade.	Arterioles. Sclerosis, grade.	Hemorrhages, grade.	Retinitis, grade.	Hemoglobin, gm. per cent.	Erythrocytes, millions.	Urea, mg. per cent.	Serum sulphate, mg. per cent.	Creatinin mg. per cent.	Albumin, grade.	Erythrocytes, grade	Casts, grade.	Phenolsulphonephthalein, per cent.	Urea clearance, cc. of blood cleared per min.†	Sulphate clearance, cc. of blood cleared per min.	
2– 5–30	....	....	....	..	....	..	..	12.6	4.10	..	....	....	0	0	0				
3–18–32	64.1	110	70	..	....	..	..	14.7	4.21	..	....	....	..	..	..	..	..	..	Roentgenogram of chest normal.
11–29–32	62.3	220	140	3	0	0	0	....	....	..	....	....	..	..	..	..	..	..	Roentgenogram of chest and head normal.
12– 3–32	60.5	160	90	3	0	1	0	....	....	16	4.9	1.2	3	0	0	60	25	9	No intravenous therapy. Water test: 1528 cc., sp. gr. 1.002.
		200	130	..	....	..	..	....	....	..	....	....	..	..	..	..	..	..	
12–20–32	....	160	110	3	0	1	1	....	4.82	22	5.7	1.3	3	0	0	..	..	..	Intravenous sucrose 20 to 25%, sucrose 20% with acacia 3%; spinal puncture, 1 lymphocyte, no protein pressure 25 to 2 cm. water, 12 cc. removed.
		205	140																
12–31–32	57.3	190	130	..	....	..	..	....	....	20	....	....	..	..	..	..	46	..	No lead in urine. Hemianopsia. Temperature 100° F.§
1–15–33	54.5	175	130	3	2	3	3	....	....	22	....	1.3	3	0	0	..	..	..	Temperature 100° F.§ Muscle biopsy, ratio 1.4, moderate increase in intimal and medial nuclei; 20% glucose and 3% acacia.
2–15–33	....	185	135	..	....	..	..	15.2	4.23	22	....	....	3	0	0	..	33	..	20% sucrose, 20% glucose with 3% acacia. Deep Roentgen therapy to pituitary.
3–20–33	53.6	215	135	..	....	..	2												
4–26–33	52.7	225	140	..	....	..	2												
9– 9–33	56.4	240	140	..	3	0	*	....	....	..	....	....	2	0	1				
11–16–33	....	230	140	..	3	0	*	....	....	28									
1–11–34	54.5	240	140	..	3	0	*												
3–14–34	54.1	210	130	..	3+	1	*	13.3	....	32	....	....	2	0	0				
5–11–34	53.6	240	145	..	3	0	*	....	....	..	....	....	2	0	0	..	..	..	Basal metabolic rate +12.
10–16–34‡	....	215	145	..	3	0	*	13.3	....	27	....	....	2	0	0	..	25	..	Fundus photograph. Roentgenogram of thorax showed heart enlarged to Grade 1.
2– 6–35	57.3	235	140	..	3	0	*	....	....	..	....	....	..	..	..	..	..	..	T.B. cervical lymph node; Roentgen therapy. Fifteen years since first noted.

* Residual, but not active retinitis.
‡ Electrocardiogram showed inverted *T* wave in Derivation I.
† All estimations "standard clearance."
§ Highest temperature in course of observation.

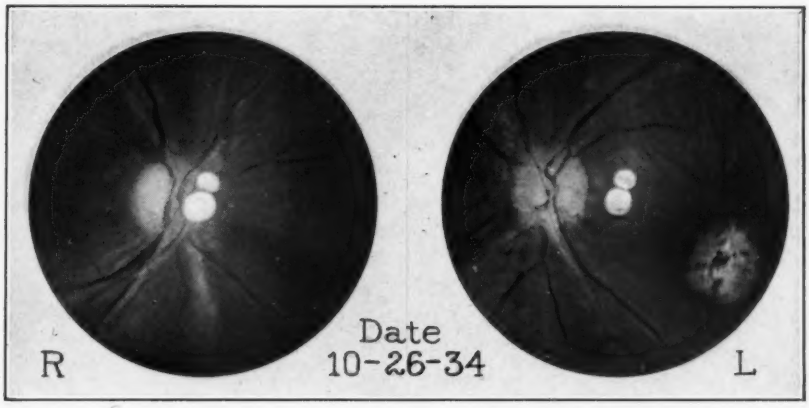

FIG. 1.—Photograph of the retina of each eye. Residual phase of acute angiospastic retinitis. Note marked narrowing and irregularity of retinal arterioles. Healed tuberculous chorioretinitis in left macula. The condition was the same in February, 1935.

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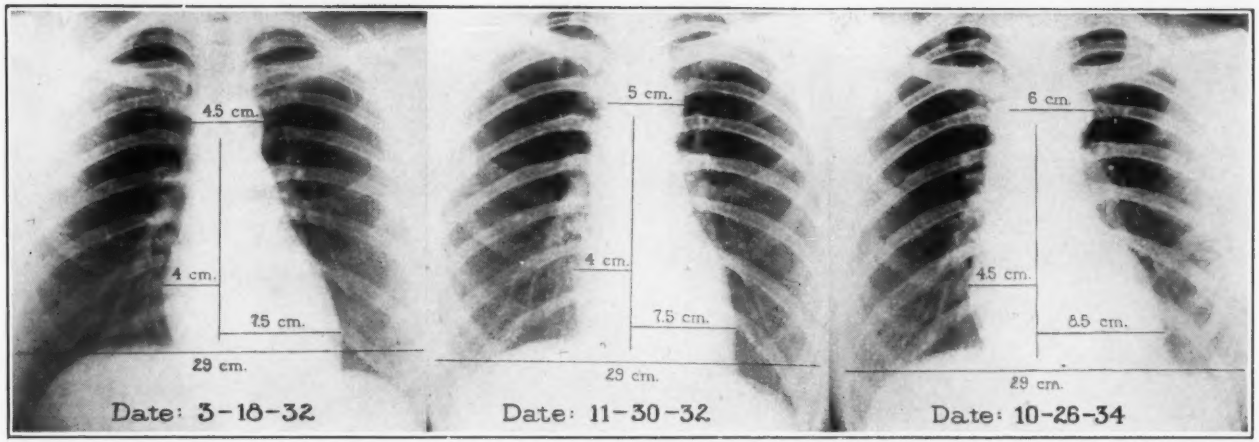

FIG. 2.—Teleoroentgenograms of the thorax. Taken as part of the routine of examination, before, at, and 2 years after, the onset of acute vasospastic hypertension. The shadow of the heart in the first photograph is of normal size; there is slight, but definite, enlargement in the third photograph.

roentgenologic treatment was administered over the pituitary gland. The woman slowly began to improve, and within a month the retinitis began to subside. The next summer she was feeling very much better.

In September, 1933, vision of the right eye was 6/7 and ability to read Jaeger 0.50. The right optic disc was slightly pale, and in both discs connective tissue was increased. The arterioles were narrowed to Grade 3, with generalized delicate perivascular sheathing, and sclerosis Grade 3. Exudate, residual from the edema, was present in the macular regions, but there were no hemorrhagic areas or cotton-wool patches.

In October, 1934, the original difficulties had not all cleared up. There were still slight residual signs of the retinitis, but it had now been more than a year since the retinitis had been active. The arterioles of the retina were still narrowed (Grade 3) and sclerosed (Grade 3), as may be seen in Figure 1. The condition had not changed at the last examination, February, 1935. The woman seemed to be in very good condition and felt well. Her weight was normal. She recognized that she was easily fatigued, but if she restricted her activities moderately, this was controlled. She slept well, and her headaches were much less frequent and not so severe as they had been. Her blood pressure on October 16 was 215 mm. systolic and 145 diastolic. There was slight but definite increase in the size of the heart (Fig. 2); the aortic second sound was accentuated to Grade 2, but murmurs could not be heard. The peripheral arteries still felt rubbery, but no more so than they had felt 2 years previously. There was albumin, Grade 2, in the urine. The value for blood urea was normal, but the urea clearance was reduced to 25 cc. of blood cleared per minute. On an electrocardiogram, the *T* wave in derivation 1 was inverted.

The patient returned to the clinic in February, 1935, because of a small lump which had become noticeable in the right parotid region. This was diagnosed as a recurrence of the previous tuberculous adenitis, and Roentgen therapy was instituted. Thus, for 15 years, the patient had had tuberculous cervical adenitis. The condition of the retinæ at this time was unchanged, and was still unchanged April 30, 1935.

Discussion. The rapid onset of retinitis, without preceding arteriosclerosis, in a case of hypertensive disease of this type, is interesting and rather difficult to explain, unless it is assumed that there is present a very acute angiospastic process similar to that seen in hypertensive toxemia of pregnancy, with resultant ischemia and anoxemia of the retina.[6] Occasionally retinitis is seen in a case of acute nephritis, but the retinitis is usually mild and transitory unless the disease goes on rapidly to the chronic stage. The retinitis in the case here reported was diffuse and severe. At the time of the onset of the retinitis, this patient had an attack suggesting cerebral angiospasm. There was, in addition to stupor and mental confusion, rather sudden, complete loss of vision of both eyes. In a few hours vision returned in the right halves of the visual fields, and in about 12 hours the fields were normal. We assumed that the loss of vision was cerebral, associated with cerebral angiospasm, and that vision returned when the spasm passed. However, it is of interest that there is a history of previous, and subsequent, attacks of migraine with hemianopsia. The striking feature in the retina, in the course of the present illness, was very marked, generalized narrowing and spastic irregularity of the retinal arterioles. The retinitis rapidly

increased in severity and diffuseness until there was a typical, so-called "albuminuric retinitis," with definite edema of the discs and generalized edema of the retina, in which macular stars gradually developed. In most cases of this type retinitis does not show a tendency to resolve,[4] whereas in this patient's case there was, after the first 6 weeks or 2 months, a very definite tendency to resolution of the retinitis. Almost 2 years after the onset, from the standpoint of retinitis proper, there was very little residual trouble. There had not been any appearance, recently, of fresh hemorrhagic areas, cotton-wool patches, or return of the edema of the retina.

Such subsidence of severe retinitis was noted by Liebreich,[1] who first described the ophthalmoscopic findings of albuminuric retinitis in 1859. Fishberg and Oppenheimer,[2] in 1930, reported in a case of malignant hypertension the healing of severe retinitis with no recurrence over a period of 4½ years. The writers reported a similar case in 1929[3] and since that date have seen 4 additional cases.

It is well recognized that retinitis does not often recur in a second attack of toxemia of pregnancy. This may be because the arteriolar walls have in some way lost their capacity for active narrowing and dilatation. The cessation of sudden variations in caliber, and their consequent interference with the circulation of the retina, may account for the gradual healing of the retinitis. The coincidence of subsidence of the retinitis with definite improvement in the general physical condition suggests, however, that the active angiospastic factor which was apparently the initial cause of the retinitis, and of the rise in blood pressure, is less active or relatively dormant.

There has been no recurrence of the acute cerebral symptoms in the last 2 years. It is difficult to ascribe such severe cerebral symptoms, and the accompanying increase in cerebrospinal fluid pressure, to an attack of migraine. The headaches have been much less severe and less frequent than before. Complaint of vertigo has not been made. Hypertension has persisted since the onset, but palpation of the peripheral arteries does not indicate distinct thickening of their walls. There never have been any clinical signs of myocardial decompensation, although last October there was evidence of myocardial injury, as indicated by inversion of the *T* wave of the electrocardiogram. Abnormal urinary findings and renal functional disturbances have persisted, as has the hypertension, since the onset. The absence of erythrocytes, even on microscopic examination, in many routine urine analyses, is noteworthy. Renal disturbances never have resulted in serious demonstrable renal insufficiency or in characteristic symptoms of renal impairment. Secondary anemia has not developed in 2 years of illness. Clinicians have observed, and have stated, that patients who have chronic tuberculous lesions rarely have increased blood pressure. In the present case, tuberculosis of the lymph nodes in both cervical chains was present many years before the onset of hyper-

tensive disease, and is still present. It is difficult to establish any definite relationship between these two conditions in the present case.

Naturally the question arises as to whether the rather intensive use of hypertonic solutions intravenously, and of Roentgen therapy, was related to the relatively rapid subsidence of serious symptoms, and the diffuse retinitis. We believe that these measures were possibly beneficial, but lack of control renders it impossible to make a categorical statement. At least, it can be said that harmful effects from these forms of treatment have not been noted.

In spite of the rather favorable course in this case thus far, we feel that the ultimate prognosis must be guarded. From the general clinical and retinal findings, we should be tempted to place such a case as this in Group 2^5 type of diffuse arterial disease with hypertension, if we performed examination for the first time in the stage of remission. This patient has adequate cardiac and renal function. She does not have edema of the discs or active retinitis. It would be difficult to say that edema of the discs ever had been present. In a few months more it probably will be difficult to determine whether this patient ever had retinitis. However, with the evidence of previous cerebral irritation and retinitis, she should be considered in the Group 3 type of diffuse arterial disease with hypertension. Further observation of this, and other similar cases, is the only method available at present for determining the ultimate prognosis.

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A SUGGESTION FOR SIMPLE TREATMENT OF ACUTE ARTERIAL SPASM.

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The part played by vasospasm of collateral channels in the ischemia of a region following acute occlusion of its major artery is receiving increasing recognition. This recognition has opened new

possibilities for the conservation of tissue. The present contribution suggests a simple method of treatment directed towards the release of such collateral vasospasm.

The effect of sympathectomy on collateral circulation after arterial occlusion has been studied in the laboratory.[1] Nystrom[3] is in agreement with the conclusions expressed by Gosset, Bertrand and Patel,[4] Denk[5] and Allen and MacLean[2] on the important influence of spasm in this condition. Gage[6] has abolished the sympathetic impulses by alcohol injection of the lumbar ganglia before ligating the common iliac artery for aneurysm, and Bird[7] has performed lumbar sympathetic ganglionectomy before operation for popliteal aneurysm. Lehman,[8] following the suggestion of Leriche,[9] has carried out arteriectomy when ligation is necessary, believing that a perivascular sympathectomy is thereby effected. Allen and MacLean,[2] following the suggestion of Denk,[5] employed papaverin as an antispasmodic to tide a patient suffering from arterial embolism over the period of active vasospasm.

Sympathectomy either by excision or by alcohol injection is, of course, the most direct and sure method of preventing vasospasm in a part. It is probable, however, that the vasospasm following sudden arterial occlusion or the mechanical stimulation of the arterial wall is transient, and such measures are therefore too radical. As is well known, the vasospasm that follows such extensive local stimulation of a bloodvessel as that incident to periarterial sympathectomy lasts only about 16 hours. Temporary vasodilatation with papaverin was apparently successful in one leg in Allen and MacLean's case. It would seem that in addition to passive vascular exercises,[10] any of the expedients employed for temporary vasoconstrictor release for diagnostic purposes could theoretically be employed for therapeutic purposes. The choice of method for simplicity, applicability and effectiveness must be determined by repeated clinical trial.

Coller and Maddock[11] showed that complete peripheral vasodilatation can be obtained even in the presence of vasospastic conditions by creating a physiologic demand for heat loss. This they accomplished by raising the general environmental temperature through the simple method of applying blankets to the body and thus preventing radiation. They proposed this method as a means of measuring the vasoconstrictor element in arterial disease accompanied by diminished volume flow of blood to a part. The adaptation of this simple diagnostic procedure to the therapy of possible vasospasm accompanying an arterial lesion was employed in the following case.

Case Report. W. M. (No. 115991), white, single, aged 17, was admitted to this hospital April 2, 1935, and discharged May 17, 1935. Four years earlier he had suffered from a perforating wound of the left thigh caused by a .22 caliber bullet and resulting in a traumatic aneurysm just proximal

to the passage of the femoral artery through the adductor magnus tendon. Occasional pain had been the only striking symptom until 4 days before admission when an acute syndrome had supervened, consisting of pallor changing to cyanosis, cramps in the calf, swelling of the foot and ankle, and pain in the region of the aneurysm. Examination on admission showed coolness and marked cyanosis of the left foot with darker reddish patches scattered over the lower leg and toes. The color changes were increased by the dependent position. There was a slight pitting edema. The left calf measured 35 cm. in circumference, the right 33.5 cm. The posterior tibial and dorsalis pedis arteries were easily identified on the left, although the pulsations were somewhat less strong than those of the corresponding vessels on the right. There was no dilatation of superficial veins. The aneurysm was firm, tender, and somewhat diffuse in outline; it presented only moderate expansile pulsation. Roentgen ray showed calcification of its walls. There was a soft systolic bruit. General physical and routine laboratory examinations were of no significance. There was no evidence of cardiac enlargement. The blood pressure ranged around 120 mm. Hg; the pulse pressure around 50 mm. The blood Wassermann and Kahn tests were negative.

The cause of the acute developments superimposed upon the old arterial lesion was never satisfactorily explained. Arteriovenous fistula, rupture of the false aneurysmal sac, massive embolism or thrombosis were all satisfactorily ruled out by pre-operative examination and the operative findings. The syndrome was made particularly puzzling by the fact that the reddish discolored patches on the calf, shin and toes eventuated in scaling or even extremely superficial loss of tissue, while the distal pulsations remained active.

A possible explanation presented itself during the period of observation, when it became evident that the patient suffered from marked generalized vasomotor instability. The local condition improved progressively with rest in bed and local heat applied by the heated foot cradle. Pain diminished, color improved except for the markedly changed patches, swelling disappeared and the aneurysm became less tender and more definite in outline. However, on at least one occasion the left leg again became blue. Examination at this time showed the right leg also and both hands to be blue, cool and moist. Surface temperature tests showed a difference of from 1° C. to 2.7° C. between corresponding areas of the two feet, the diseased foot being the warmer. It was therefore thought possible, as an explanation of the acute syndrome, that a small embolus, detached from the aneurysm and lodging in an artery distal to the level of ordinary vessel palpation, might have resulted in an attack of local vasospasm, exaggerated by general vasomotor instability to a degree sufficient to cause actual though slight tissue necrosis before gradual relaxation of the vessels.

This observed attack of generalized vasoconstriction further suggested the danger of such an attack following operation on the aneurysm. The vasomotor response to sympathetic paralysis was therefore tested prior to operation under spinal anesthesia, partly in order to measure the reaction that could be expected if intervention on the sympathetic function seemed to be indicated after operation on the aneurysm, and partly as a matter of clinical interest in a case presenting a local organic arterial lesion together with vasomotor instability. Normal vasodilatation levels were observed in both legs.

After 17 days of observation the aneurysm was exposed and entered under spinal anesthesia and a tourniquet. A lateral opening in the femoral artery was found, leading into a false aneurysmal sac about 4 inches in diameter, filled with old degenerated and partly organized blood clot. The wall of the sac was thick and contained much calcium. There

had been no recent rupture or bleeding into the sac itself. A typical restorative endoaneurysmorrhaphy was done with preservation of the entire sac wall. In closing the opening into the artery, the tissues were so badly scarred and calcified that only rather deep bites of the needle would prevent cutting out of the silk sutures. It was therefore feared that the lumen of the femoral artery might have been somewhat narrowed.

The patient was examined as soon as complete sensation had returned to the feet. The left foot was paler, more cyanotic and cooler than the right. Arterial pulsations were present in the right foot and ankle and absent in the left. Capillary return on the left was somewhat slow. Differential diagnosis lay between occlusion of the femoral artery by suture, and vasospasm from mechanical stimulation of the arterial wall. The leg and foot were thickly wrapped in a roll of absorbent cotton. For about an hour there was no improvement in appearance. The patient was then wrapped up to the neck in two blankets and a body cradle, warmed with electric light bulbs, was placed over him. The local improvement after this procedure was striking. Within less than an hour the foot was warm and pink and within 2 hours the pulsation of the dorsalis pedis artery could be perceived. At this time the patient noted that the foot and leg felt better than at any time since the original injury 4 years earlier. The body temperature was recorded at frequent intervals during the period of immediate postoperative observation. The highest temperature reached within the first 24 hours was 99.4° F. by mouth. The elevated environmental temperature was maintained for about 36 hours.

Convalescence was thereafter uncomplicated except for persistent blueness of both feet when the patient was first allowed to sit up. This was definitely worse in the left foot. It was overcome by postural exercises with carefully graduated activity. The wound healed *per primam.*

It has long been established surgical practice to protect an ischemic extremity from heat loss by bandages of cotton-wool and the application of external heat with hot-water bottles or with warm air from electric lights beneath a cradle. The rationale of this procedure has probably two elements. In the first place, it is hoped that the conservation of heat may delay necrosis until collateral circulation is established. In the second place a reactionary hyperemia is hoped for from local vasodilatation such as occurs when the hand is immersed in hot water.

To create a physiologic demand for heat loss by increasing the general environmental temperature is perhaps more logical in view of its proven effectiveness in vasospastic conditions[11] and certainly not more complicated or difficult than to wrap the involved extremity alone. In the case cited there is no proof of its effectiveness; there is, however, reason to assume its effectiveness.

The suggestion is made, therefore, that in all cases of suspected acute vasospasm the principle of Coller's diagnostic test be applied therapeutically. Coller[12] states that he does not know of any such application previously and no reference to it has been found in the literature. If further clinical experience confirms the benefits, expected *a priori* and perhaps demonstrated in this case, this method may become one, among others (such as the use of vasodilator drugs and of passive vascular exercises) to be chosen when sympathectomy is not justified.

Specifically it is suggested that all patients suffering from arterial embolism and all patients in the period immediately following operations on the arteries be exposed to increased general environmental temperature by being enveloped in blankets as a primary treatment. This procedure will serve to fix the value of the method and may easily prove of enormous benefit to individual patients.

Conclusion. 1. Vasospasm of collateral channels in acute arterial occlusion and following surgery on the arteries is being emphasized in surgical thought.

2. The control of such vasospasm by sympathectomy is certain but radical.

3. Simple methods, such as vasodilator drugs and passive vascular exercises, have been used for control of vasospasm successfully.

4. It is suggested that Coller's diagnostic test for vasospasm (elevation of the environmental temperature) may have therapeutic possibilities in this connection. A case is presented which tends to confirm the suggestion.

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A STUDY OF THE VENOUS BLOOD PRESSURE IN SOME COMMON DISEASES.

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Cardiac failure with congestion is of frequent occurrence and easy of diagnosis. It may be recognized by the presence of breathlessness, engorgement of the veins, enlargement of the liver, cyanosis, peripheral edema, ascites and edema of the lungs. Much attention has been paid to many of these phenomena, but not to the study of the veins which frequently affords the first signs of circulatory breakdown. "Direct measurement of the venous pressure," writes Sir Thomas Lewis,[1] "will often provide an invaluable guide to the patient's state; repeated readings will often indicate clearly the course of the malady." The present paper was prepared in order to emphasize the value of measuring the venous blood pressure at the bedside. In the pages which follow, the term "congestive heart failure" will be used in the sense defined above. The criteria for diagnosis of the several heart disorders described are, in the main, set forth by Lewis[1] and will be given in more detail under the appropriate headings.

Methods. The direct method of Moritz and von Tabora, as modified by Griffith, Chamberlain and Kitchell,[2] was employed. The desired vein (usually the antecubital) was punctured with a needle and the saline solution filling the manometer tube was allowed to run into the vein until a stationary level was reached. The readings were obtained directly in millimeters of water (for practical purposes the specific gravity of 0.9% NaCl is the same as that of water). It may be necessary at times to correct for the capillary action of the tube, but with the particular apparatus used this correction was negligible. The determinations were made whenever possible under basal conditions, the patient lying in the dorsal position with the vein at the level of the right auricle which is at the midaxillary line. This procedure was impossible with many of the cardiacs, so that in these cases the readings were taken with the patient in the sitting position with the arm elevated to the level of the right auricle. In this manner comparable measurements were obtained. Serial determinations were made at intervals on many of the heart patients to observe the course of their disease.

Findings. The material which forms the basis of this paper consists of 366 determinations of the venous blood pressure of 215 patients. Early in the study all cases admitted to the medical wards were tested, but as the work progressed only cases of especial interest were chosen.

The results have been arranged graphically so that one may quickly grasp the important features. In the charts (Nos. 1, 2, 5, 6, 7) each venous pressure determination has been represented by

an open circle if the patient presented no clinical evidence of cardiac failure with congestion or by a closed circle if the signs of congestion were present. Repeated determinations on the same patient have been placed beneath one another in the same vertical line. If a patient died, a small cross has been placed just above the reading which was made nearest to the time of death. By observing whether the circles are closed or open and whether in the upper or lower portion of the charts, one may correlate at a glance congestive heart failure with elevation of venous pressure.

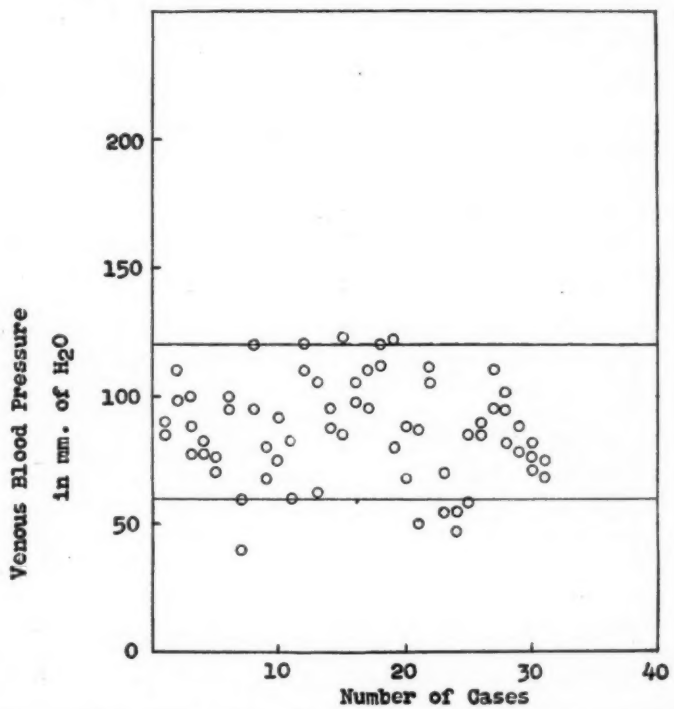

CHART 1.—The control series. Duplicate venous pressure determinations in 31 patients with a normal circulation. The area between the two parallel, horizontal lines is the zone of normal variation.

Control Series. Thirty-one patients who were known not to have presented evidences of circulatory involvement were used as a control group. Duplicate readings were made on these subjects on successive days under basal conditions. The average venous blood pressure for the control series was 83 mm. of H_2O and the mean difference of the two readings with the standard deviation of the difference was 16 ± 11 mm. of H_2O. For the purposes of this paper normal venous pressure is assumed to lie between 60 mm. and 120 mm. H_2O, which are the limits usually accepted.[2,3]

Arteriosclerotic Heart Disease. It was found convenient to accept an etiologic classification of the diseases of the heart, which have been divided into (1) arteriosclerotic, (2) rheumatic and (3) miscellaneous diseases of the heart, including cases of syphilitic and bacterial origin.

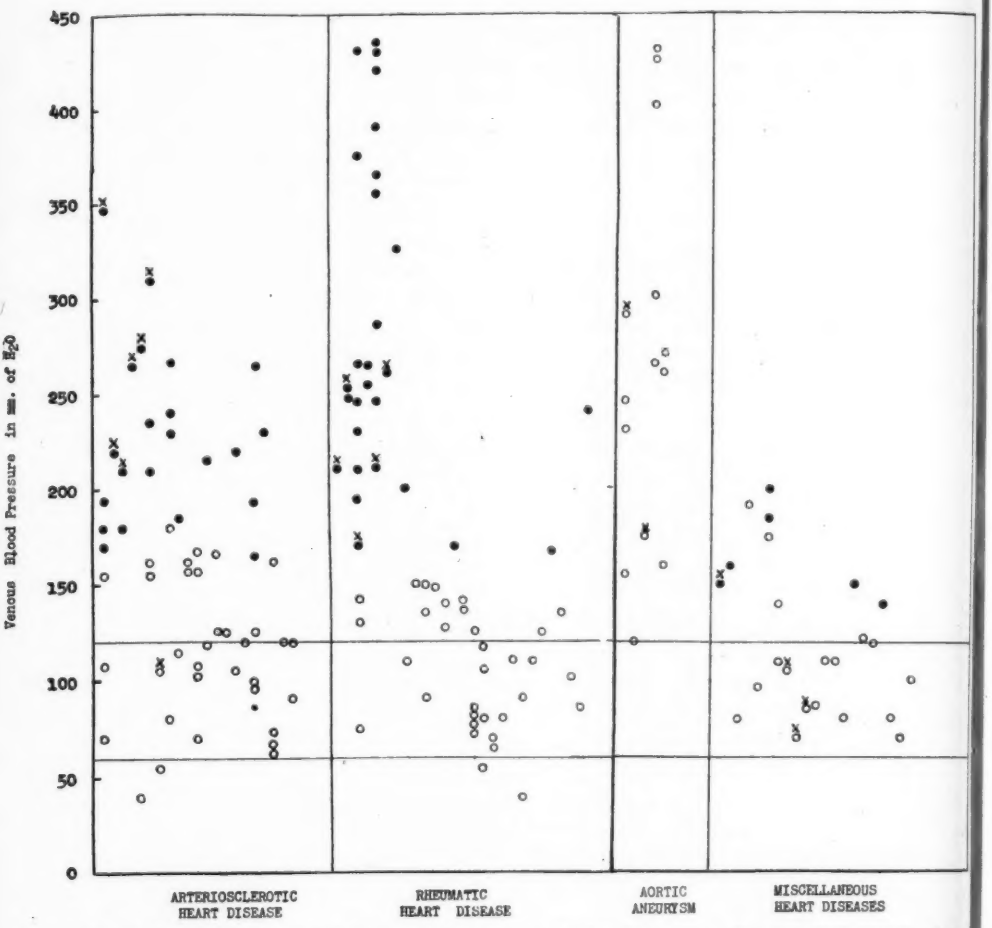

CHART 2.—Behavior of the venous blood pressure in heart disease. Cases with congestive heart failure are represented by solid circles and those without congestive failure by open circles. Serial readings are placed beneath one another in the same vertical column. A cross has been placed over the reading taken nearest to the time of death in the fatal cases. The area between the two horizontal lines is the zone of normal variation. The number of cases is plotted along the abscissa.

The arteriosclerotic group consisted of 20 cases. Many of them were cases of coronary thrombosis in which the diagnosis was made either at autopsy (4 cases) or on the presence of such typical findings as protracted anginal pain and the manifestations of collapse and

cardiac failure. Delayed signs such as fever, leukocytosis, pericardial friction rub and evidences of embolism sometimes occurred. Changes in the electrocardiogram such as plateau formation, high take-off or inversion of the *T* wave in one or more leads, and an absence of the *Q* wave in Lead IV were observed in many subjects.

Also included were some cases of essential hypertension with evidences of cardiac involvement. There were signs of hypertrophy of the heart, especially of the left side; accentuation and reduplication of the first sound at the base of the heart; gallop rhythm at the apex; and systolic murmurs at the base. There were no signs of primary inflammation of the kidneys, intracranial pressure, suprarenal tumor or chronic lead poisoning. A few individuals had suffered vascular accidents of one sort or another.

Several elderly patients were encountered in whom the diagnosis of chronic arteriosclerotic heart disease ("chronic myocarditis," "senile heart," etc.) was made. They usually complained of pain over the precordium and breathlessness on exertion. Examination of these patients revealed some or all the following signs; auricular fibrillation, heart block, bundle-branch block, gallop rhythm, pulsus alternans or inversion of the *T* waves in the electrocardiographic record.

Inspection of Chart 2 shows that cardiac failure with congestion occurred frequently in arteriosclerotic heart disease and was invariably accompanied by an elevation of the venous blood pressure. Of the 20 patients studied, 8 (40%) died, while of the remainder, 11 (55%) improved sufficiently to be discharged. The behavior of the venous pressure was typical (Chart 3, Case 1). It consisted of a gradual and prolonged increase in pressure, ending in a sudden rise, due probably to terminal dilatation of the right side of the heart, death following rapidly thereafter.

A moderate elevation of venous pressure was found in some patients (150 to 200 mm. H_2O) without other signs of congestive heart failure. These cases may be followed with serial readings to great advantage as they form a class which may be called "the potentially decompensated," since they possess all the potentialities of heart failure and are indeed living beneath the sword of Damocles.

The cases which, although presenting evidences of cardiac failure with congestion on admission, improved with appropriate therapy, showed a definite decrease in the venous blood pressure until a normal level was reached. Upon the ability of the patient to maintain this normal level of venous pressure depended his future well-being (see Chart 3, Case 2).

Rheumatic Heart Disease. Heart failure with severe congestion and a high venous pressure was encountered most frequently in rheumatic carditis. The present series includes cases of chronic rheumatic heart disease as well as some examples of acute rheumatic fever with signs of early mitral stenosis. The diagnosis of rheumatic

heart disease was made only if the history indicated clearly an attack of acute rheumatic fever* during childhood or adolescence, and if the usually accepted evidences of mitral valvulitis were present. Simultaneous involvement of the aortic valve was noted in some cases. A few patients with acute rheumatic fever, but without signs of cardiac disturbance were also included for purposes of comparison.

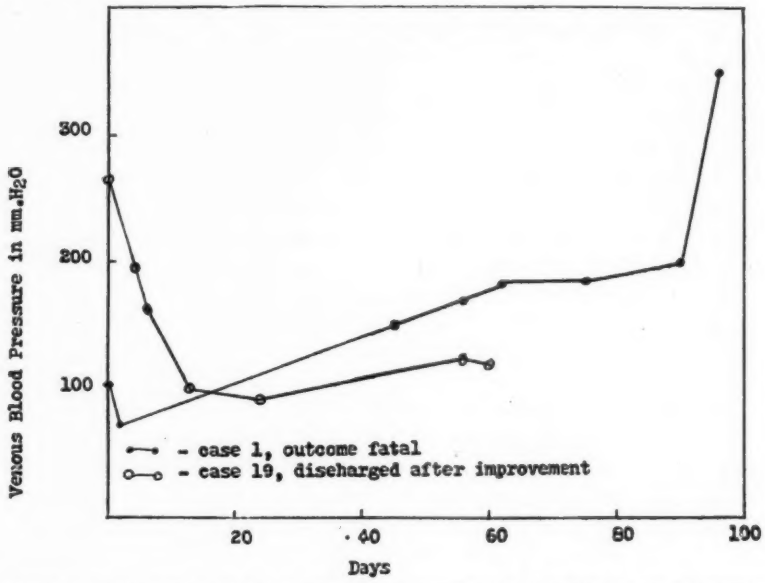

CHART 3.—The course of the venous blood pressure in 2 typical cases of arteriosclerotic heart disease.

Of 28 patients studied, 4 (14.3%) died. The deaths occurred in those patients with a pronounced elevation of venous pressure and congestive failure of the heart. The characteristic feature of the venous pressure in these fatal cases was that it could not be reduced to a normal level and subsequently maintained there (Chart 4). The individual venous pressure readings of the rheumatic fever group have been recorded in Chart 2. It will be observed that cardiac failure with congestion often ensued when the venous pressure rose above 150 mm. H_2O. One case was of especial interest, for although the patient showed marked clinical improvement, the venous pressure did not change. On the basis of this finding a grave prognosis was given. Several days later death occurred quite suddenly.

The value of serial determinations of venous pressure in following the course of rheumatic heart disease is well illustrated in Chart 4.

* The term "rheumatic fever" is used here in the wider sense of the rheumatic state.

Venous Blood Pressure in mm. of H_2O

This patient, a woman in middle life, was admitted to the hospital suffering from congestive failure of the heart. Her condition was desperate. She was bled 500 cc. and the venous pressure which had previously been near 400 mm. H_2O immediately dropped to 240 mm. H_2O with great relief of symptoms. Improvement continued during the 3 weeks she remained in the hospital and at the time of her discharge the venous pressure was 65 mm. H_2O. Under

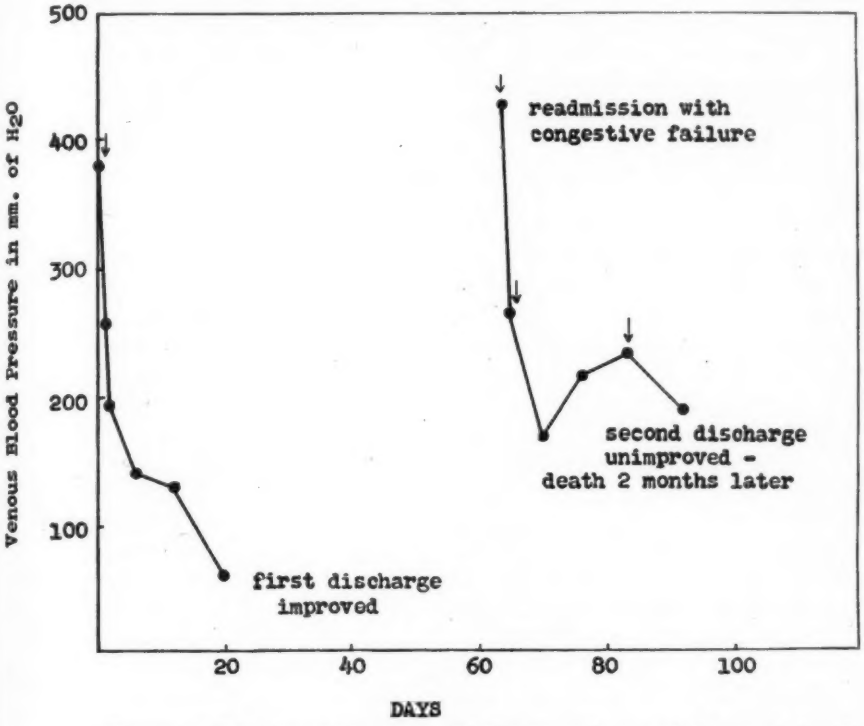

CHART 4.—Behavior of the venous blood pressure in a typical case of chronic rheumatic heart disease with mitral stenosis, auricular fibrillation, anasarca, and congestive failure. The good response to treatment on the patient's first admission is in contrast to the poor response on her readmission. The case is described in detail in the text. The arrows indicate phlebotomy.

adverse living conditions at home, circulatory failure recurred, obliging the patient to again seek hospital treatment. The venous pressure on this admission was 430 mm. H_2O; just 6 weeks after her former discharge. Phlebotomy was performed, but without giving much relief, although the venous pressure fell nearly 150 mm. H_2O. During the course of the second admission the venous pressure remained fixed between 200 and 240 mm. H_2O. Dyspnea, cyanosis and ascites persisted notwithstanding the use of digitalis, various diuretics and the paracentesis needle. At the end of a month the patient voluntarily left the hospital; 2 months later she died.

Many victims of rheumatic fever were admitted to the wards suffering from obvious heart failure with congestion. Repeated observations of the venous pressure of these individuals afforded an accurate indication of the degree of cardiac failure and a reliable estimate of the immediate prognosis. The test was also of great value in choosing the proper cases for venesection. In the presence of congestive heart failure with a venous pressure of 200 mm. H_2O, or higher, the patient was bled 400 to 600 cc. unless a marked anemia contraindicated the procedure. If the pressure in the veins fell immediately, symptomatic relief followed promptly and the patient recovered from the attack. If, on the other hand, the venous pressure was not lowered by bleeding, then the prognosis was ominous.

Aneurysm of the Aorta and Other Mediastinal Masses. The cases with aortic aneurysm were of peculiar interest. Of 4 cases observed, 3 showed a marked elevation of venous pressure. The clinical appearance of these patients was remarkable (Chart 2). Picture to yourself a patient with a high venous pressure who does not present signs of cardiac failure, but, instead, is able to walk about the ward without great effort; who complains more of headache and throbbing of the bloodvessels than of dyspnea and edema. There is only one lesion which may cause such a syndrome: a mediastinal mass obstructing the return of blood to the right auricle. The presence of an aneurysm, as in these cases, is easily demonstrated by fluoroscopic examination and confirmed by a positive Wassermann reaction. Other mediastinal masses besides aneurysm may, of course, give rise to similar findings. Thus Case 5 was a young boy suffering from Hodgkin's disease, in whom the Roentgen ray revealed huge mediastinal masses. The venous pressure was 265 mm. and 255 mm. H_2O on two different occasions. After intensive Roentgen ray therapy the masses disappeared and the venous pressure fell to 160 mm. H_2O.

It is worthy of note in Chart 2 that although many of the cases with mediastinal masses had an excessively high venous pressure, none showed signs of congestive heart failure. In 1 of the patients with an aortic aneurysm the venous pressure was normal. This was interpreted to indicate little or no encroachment of the mass upon the superior vena cava or right auricle of the heart.

Miscellaneous Disorders of the Heart. This group includes several diverse conditions (Chart 2). There were 7 cases of syphilitic heart disease in which the diagnosis was made on the findings of a positive Wassermann reaction, signs of aortic regurgitation, and in some cases of a failing circulation. Four cases of subacute bacterial endocarditis were encountered showing positive blood cultures, embolic phenomena, continued fever, clubbed fingers, splenomegaly, and clear evidence of heart disease. Three of the patients died and the diagnosis of subacute bacterial endocarditis was verified at autopsy.

In each case death occurred from cerebral embolus. There were also a number of cases in which cardiac disease was present either with or without failure and congestion, but in which a definite etiologic diagnosis could not be made.

All these cases may be quickly dismissed after remarking that a high venous pressure was observed only in the presence of congestive heart failure (Chart 2).

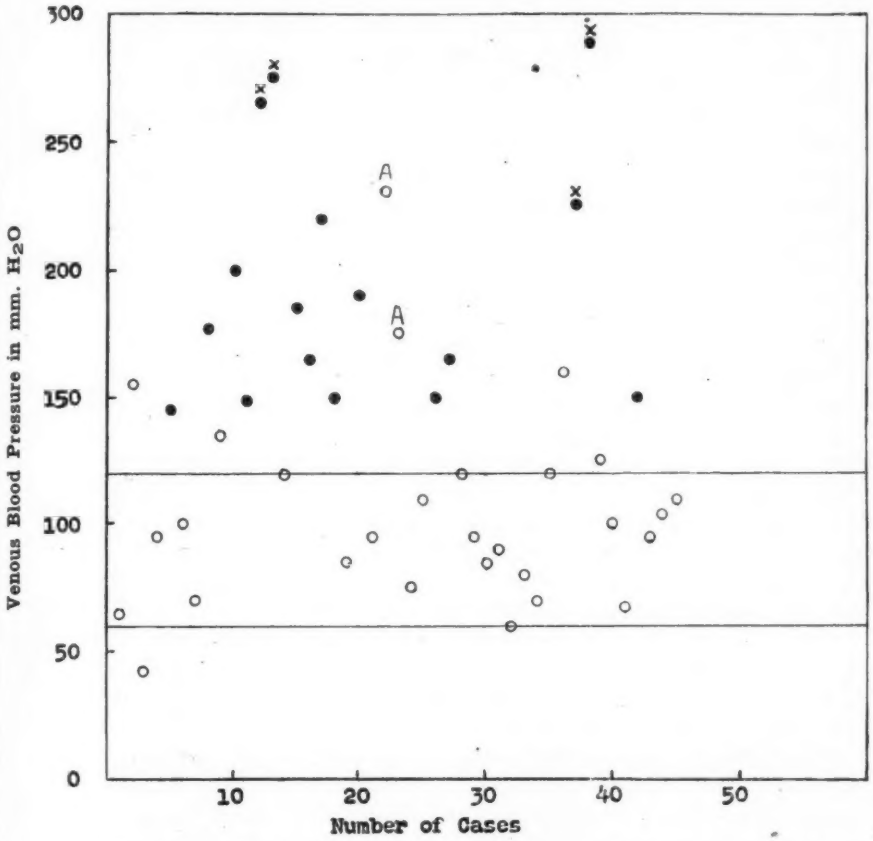

CHART 5.—Behavior of the venous blood pressure in hypertension. Symbols as in Chart 2. The letter "A" has been placed over 2 cases of aortic aneurysm, in which condition a high venous pressure may occur without signs of congestive heart failure.

Hypertension. The mutual relationship of the arterial and venous blood pressures has interested investigators since the time of the Rev. Stephen Hales (1732). In the present study 44 cases were encountered with a systolic pressure of 150 mm. Hg, and a diastolic pressure of 100 mm. Hg or higher. The average arterial pressure of these cases was 185/106 mm. Hg, and the average venous pressure

136 mm. H_2O. It will be noted that the average venous pressure was slightly above the upper normal limit. Inspection of Chart 5 explains this apparent increase of venous pressure in hypertension. It is seen that the high readings are represented by solid circles, indicating that the patients showed clinical evidences of cardiac failure with congestion. This was, of course, to be expected, for congestive heart failure is a frequent termination of many cases of hypertension. If the cases with congestion were omitted from the calculation, the average venous pressure would be 111 mm. H_2O, an entirely normal figure, whereas the arterial pressure would remain at 188/106 mm. Hg. Attention may also be drawn to the cases of rheumatic heart disease where exceedingly high venous pressures occur frequently, although the arterial pressures are uniformly low. The evidence at hand indicates that in cases of hypertension due to any cause whatsoever, an elevation of the venous blood pressure appears only with the onset of congestive failure of the heart and is probably one of the earliest signs of such an occurrence. This concept of the independence of the venous and arterial blood pressures has been accepted by many recent workers and is supported by much experimental work.[4–10]

Thyroid Disease. It is perhaps not amiss to mention in this place those patients suffering from thyrotoxicosis, for each of them is a case of potential heart disease. Fifteen patients were examined whose complaints were of sufficient severity to require hospitalization. The signs of toxicity consisted of an increase in the metabolic rate, nervousness, loss of weight, exophthalmos, and a thyroid mass. In some cases there were also disturbances of the circulation, such as tachycardiac, vasodilatation, auricular fibrillation, anginal pain and the usual evidences of cardiac failure.

Chart 7 shows that an increase in venous pressure was seen only in the presence of congestive cardiac failure. The venous pressure level was also of value in determining the length of the pre-operative treatment in the patients selected for operation.

Disease of the Respiratory System. The influence of disorders of the respiratory system upon venous pressure is of great interest, since their differentiation from circulatory disturbances may be difficult. Three common respiratory diseases were studied, pulmonary tuberculosis, bronchial asthma and lobar pneumonia (pneumococcus, see Chart 6). The average venous pressure for all the cases tested was 120 mm. H_2O, which is a high normal value. When a definite elevation of venous pressure occurred, as it did in 15.4% of the total cases, it was usually accompanied by some evidence of circulatory embarrassment. One of the tuberculosis patients had a marked shift of the heart to the right following pneumothorax and another showed cardiac hypertrophy. On the wards the determination of the venous pressure proved to be an easy and reliable means of differentiating between cardiac and respiratory disorders.

Miscellaneous Diseases. A large variety of diseases was studied during the course of this investigation and the venous blood pressure determinations have been recorded in Chart 7. The results are remarkable for the fact that a significant elevation of venous pressure was found only in patients suffering from congestive failure of the heart. The only exceptions to this were certain cases of mediastinal masses in which the increase in pressure has been already described. In all other cases the venous pressure was within normal limits and remained so unless cardiac failure threatened.

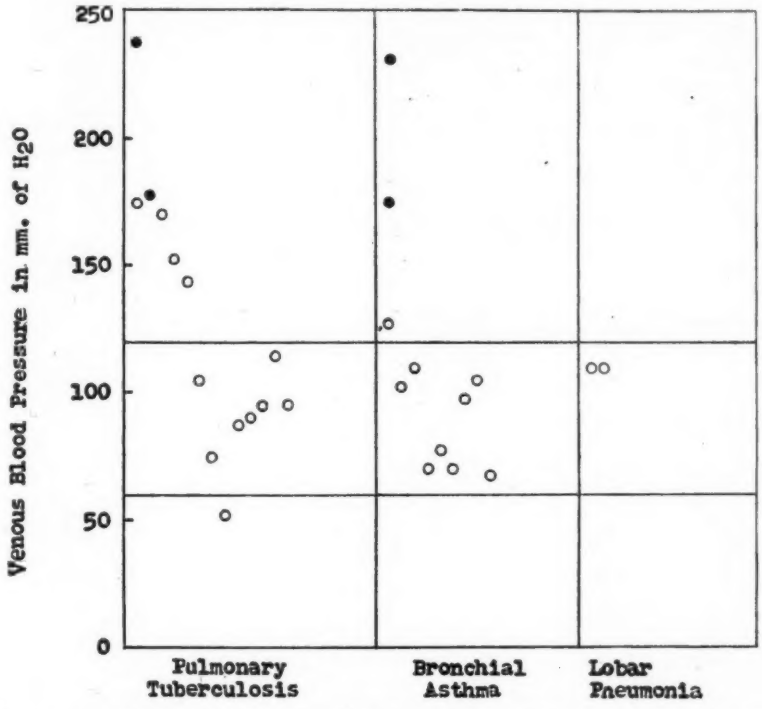

CHART 6.—Behavior of the venous blood pressure in diseases of the respiratory system. The symbols are the same as in Chart 2.

Discussion. The records of a large number of patients have been presented in order to illustrate the value of routine determinations of the venous blood pressure in certain cases. The outstanding finding has been the increase in venous pressure in congestive failure of the heart and in some cases with an aortic aneurysm or other mass within the mediastinum. The venous pressure in these conditions has been sufficiently high to stand in marked contrast to the normal pressure in diseases in which circulatory failure did not occur. This relation held in disorders of the respiratory system as well as for cases with hypertension. Whenever a high venous

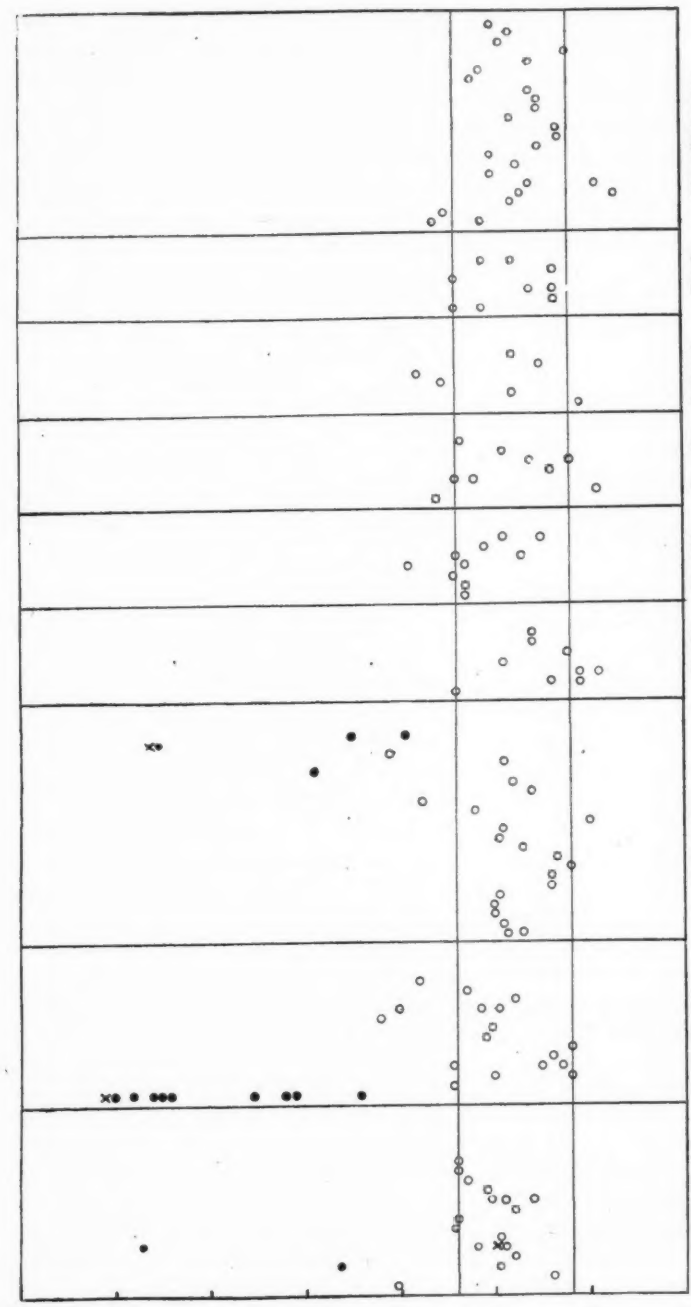

CHART 7.—Behavior of the venous pressure in some diseases. The symbols are the same as in Chart 2. Note the absence of a high venous pressure save in the presence of heart failure with congestion.

pressure was discovered, unless due to a mediastinal mass, it indicated a failing heart and constituted one of the early signs of congestion.

There are always on hospital wards cases which present exceptional problems of diagnosis. In these patients a venous pressure determination may be of much help. It will be recalled that an increased venous pressure in 3 of the cases with aortic aneurysm

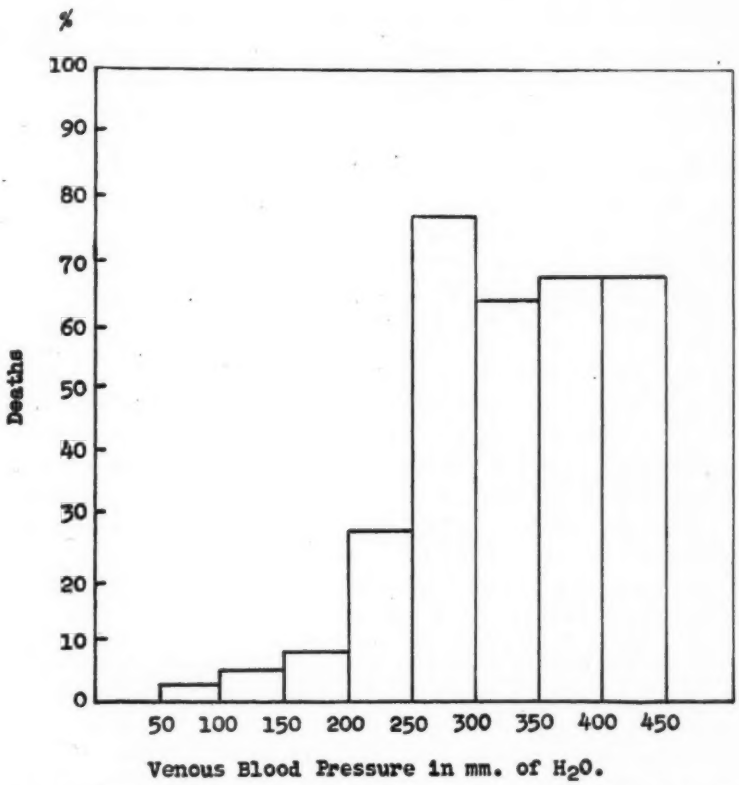

CHART 8.—Distribution curve for the deaths from all causes. Note the marked increase in mortality when the venous pressure was above 250 mm. of H_2O.

was the first indication of a lesion of the circulatory system. The importance of knowing the venous blood pressure was further emphasized by the chance admission on the same day of 3 patients in coma and with signs of a cerebral lesion on the right side. In the first 2 patients the venous pressure was normal and a diagnosis of brain tumor was made. At necropsy, 1 case was found to have a glioma in the right frontal lobe and the other an abscess in the same region. When the third patient was admitted with similar findings, the same diagnosis was made. However, in this case the

venous pressure was elevated on 2 occasions (183 mm. and 210 mm. H_2O) and it was suggested that the patient was suffering from circulatory collapse. The patient died shortly, and at the autopsy the coronary arteries were seen to be completely occluded, the right side of the heart was greatly dilated, the lungs were edematous, and the liver the seat of chronic passive congestion. The brain was normal in appearance.

The value of serial determinations of the venous blood pressure in estimating the efficiency of therapeutic measures has been stressed by many writers.[11–16] The results of this study have amply justified this attitude. There is no other procedure which so easily and accurately affords an estimate of the cardiac reserve in disease.

The prognostic significance of venous pressure measurements has been unfortunately neglected. In Chart 8 the death rate from all causes has been plotted, the highest venous pressure reading for each case having been used in the calculations. The striking feature of the results is the great increase in mortality when the venous pressure rose above 250 mm. H_2O. Among the patients with a venous pressure of 250 mm. H_2O or higher the mortality was 69%, whereas it was only 8% among those whose pressure remained below the critical level of 250 mm. H_2O.

In conclusion a few personal remarks may be permitted. The recent journals contain many excellent papers which indicate the value of measuring the venous blood pressure in patients with cardiocirculatory disease; but in spite of the unanimity of opinion, full advantage has not been taken of this valuable test. The technique is easy; the normal range and behavior of venous pressure in disease are well known. Perhaps the inertia is to be explained by a natural hesitancy to accept procedures which are not customary. However, a cure for the disease is easily effected by learning the technique of the test and applying it in suitable cases. The results of "taking the cure" have been once more described. We have been so impressed with the value of the test that venous pressure determinations are now made on all cardiac cases admitted to the medical service.

Summary. 1. The results of 366 determinations of the venous blood pressure in 215 patients suffering from various diseases have been presented.

2. In a control series of 31 patients who showed no evidences of circulatory disease, the average venous pressure was 83 mm. H_2O and the difference of the two readings with the standard deviation of the difference was 16 mm. $H_2O \pm 11$ mm. H_2O.

3. An increase in venous pressure was observed only in patients suffering from cardiac failure with congestion or mediastinal obstruction.

4. Serial determinations of the venous pressure were of value in following the course of cardiac cases; a shift towards the normal indicated a favorable prognosis, but a progressive increase in pressure was an unfavorable sign.

5. The arterial and venous blood pressures appear to be independent, in the sense that a change in one does not necessarily affect the other.

6. The presence of pulmonary tuberculosis, bronchial asthma or lobar pneumonia did not influence the venous pressure of the cases studied.

7. When an increase in venous pressure occurred in any disease, it usually indicated beginning circulatory failure.

8. Of the patients with a venous pressure over 250 mm. H_2O, 69% died within 3 months, whereas only 8% of those with a pressure below this critical level succumbed.

In the preparation of this paper I have profited greatly from the kind criticism of Dr. Edward L. Bortz, Chief of Medical Service "B," the Lankenau Hospital. On his service this work was initiated and largely carried to completion. Dr. Fred L. Hartmann, Chief of Medical Service "A," has placed the records of several of his patients at my disposal.

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THE DEMONSTRATION OF COLLATERAL VENOUS CIRCULATION IN THE ABDOMINAL WALL BY MEANS OF INFRA-RED PHOTOGRAPHY.

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Infra-red photography has been used experimentally, mostly in astronomy, for many years. Only recently the production of plates that are sufficiently sensitive to the infra-red rays to permit short exposures has made possible the use of this method on a wider scale. Clark[1] says that this method of photography has been found of value in certain European hospitals as a diagnostic aid in certain types of skin diseases. He also records that European workers have found that varicose veins which were not visible to the eye have been demonstrated by this method. Recently Barker and Julin[2] and Payne[3] have shown the value of this technique in demonstrating the superficial venous system of man. Payne concludes that veins can be made visible by this means when they cannot be seen nor recorded upon the ordinary photographic plate. On the other hand Barker and Julin believe that it is doubtful if veins can be shown by infra-red plates which cannot be seen by the naked eye. These authors credit Rawling with the suggestion that infra-red photography might find some application in medicine. To him is also attributed the finding that the skin has its maximum transmission in the part of the spectrum wherein are found the infra-red rays. This fact together with the fact that the blue color of the veins is absorbed by the filter used in the infra-red technique and thus made to appear dark on the infra-red (positive) plate, explains why the veins can be so graphically demonstrated by this method of photography.

In view of the excellent portrayal of superficial veins by this method it seemed to us to be worthwhile to attempt some use of this procedure in the hope that it would aid in the early recognition of the collateral circulation in cases suspected of early portal obstruction. As this is a frequently debated question, we have photographed the abdominal wall in a number of cases in which this question arose.

Case Reports. I. Cases with Proved Cirrhosis.

Case 1.—M. B., a white woman, aged 47, entered Strong Memorial Hospital with the complaint of enlargement of the abdomen and loss of weight. The history records two attacks of painless jaundice during the preceding year and the loss of about 20 pounds in weight during this time.

There were definite signs of fluid in the abdomen. After paracentesis the liver edge was felt slightly below the costal margin. The spleen was not palpable. One observer noted enlarged superficial veins in the abdominal wall. A diagnosis of cirrhosis of the liver was considered most likely, although the attacks of painless jaundice which had cleared up suggested the possibility of obstruction of the common bile duct by a stone. The venous network could not be seen in an ordinary photograph of her abdomen; an infra-red photograph (Fig. 1) revealed evidence of venous distention out of proportion to that seen by the naked eye. The patient became comatose and died 17 days after admission. An autopsy revealed extensive cirrhosis of the liver. There is no statement about the state of the veins in the autopsy record.

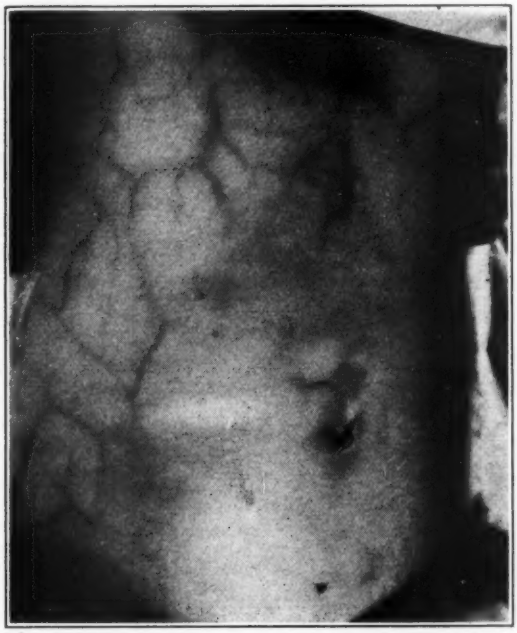

FIG. 1.—Infra-red photograph of abdomen of patient with proved cirrhosis of the liver.

II. CASES WITH PROBABLE CIRRHOSIS.

CASE 2.—A. M., a white woman, aged 50, entered Rochester Municipal Hospital with the complaint of weakness and loss of weight for about 1½ years. Because of language difficulties no adequate history was obtained. The significant findings were: evidence of recent weight loss, deep jaundice, a greatly enlarged liver, a barely palpable spleen and ascites. The liver edge was palpable slightly below the level of the umbilicus; it was firm, questionably finely nodular and not tender. Moderate distention of the superficial veins of the abdominal wall was noted by several observers. A diagnosis of cirrhosis of the liver seemed most likely although metastatic infiltration of the liver from some intraäbdominal neoplasm was recognized as a possibility. Roentgenologic studies of the gastro-intestinal tract revealed no evidence of neoplasm. An ordinary photograph (Fig. 2) of this patient's abdomen revealed nothing at all in the way of veins; an infra-

red photograph (Fig. 3) revealed strikingly the pattern of the superficial veins, the largest and most numerous of which were in the flanks. The patient gradually became comatose and died. Permission for autopsy was not obtained.

CASE 3.—G. H., a 62-year-old white man, who had been a heavy drinker for many years, was admitted to the Rochester Municipal Hospital with the complaint of enlargement of the abdomen for a period of a month. After paracentesis a hard liver edge could be felt about 5 cm. below the costal margin. The spleen was not felt. One observer made the note that there was no evidence of collateral circulation in the abdominal wall, while a second observer on the same day made the note that there were definitely visible veins forming a caput Medusæ about the umbilicus. An infra-red

FIG. 2.—Ordinary photograph of abdomen of patient suspected of having cirrhosis of the liver.

photograph (Fig. 4) showed the veins to be definitely more visible than those seen in any normal abdomen. The diagnosis of cirrhosis of the liver seemed highly probable. The patient was discharged from the hospital with instructions to return at intervals for abdominal paracentesis.

CASE 4.—M. F., a white woman, aged 52, was admitted to the Rochester Municipal Hospital with the complaint of a sensation of epigastric fullness for a period of about 13 weeks. The history was quite inconclusive. The only physical finding of apparent value was a considerably enlarged liver which felt firm and smooth. There was no visible evidence of enlarged collateral veins in the abdominal wall. An infra-red photograph, however, showed them to be considerably more extensive than in our controls. She was discharged in the same condition as on admission.

CASE 5.—C. P., a 46-year-old white man, entered Strong Memorial Hospital with the complaint of pain across the upper abdomen for $3\frac{1}{2}$ years. Associated with this he had had varied complaints of indigestion. There

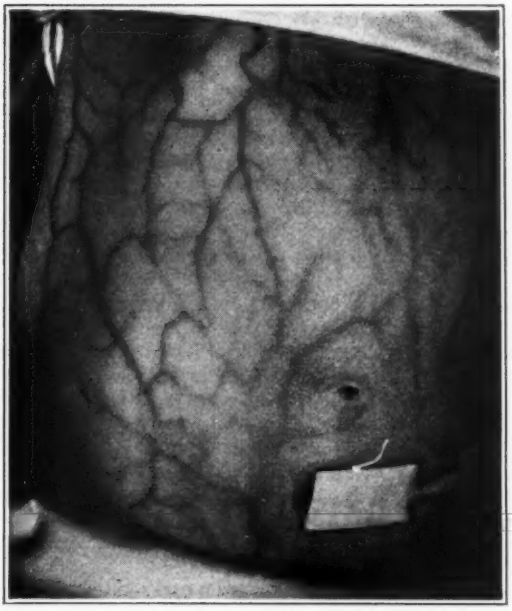

FIG. 3.—Infra-red photograph of abdomen of same patient as in Fig. 2.

FIG. 4.—Infra-red photograph showing an increase in number and size of veins in a patient suspected of having hepatic cirrhosis.

was a history of tarry stools at onset of his illness. Physical findings were essentially negative. However, a Roentgen ray of his abdomen revealed that the spleen was enlarged and that the liver appeared to be smaller than normal. The patient then recalled that at one time his family physician had told him that there was a mass lying to the left of his stomach. The spleen was not felt by us, however. There was no visible evidence of increased collateral venous circulation noted, but an infra-red photograph showed venous channels more extensive than those of our controls. The patient was discharged from the hospital unimproved.

CASE 6.—J. S., a 55-year-old Italian man, was admitted to the Strong Memorial Hospital with the complaint of stomach trouble. This began 3 months before admission and consisted of soreness in the right upper part of his abdomen and frequent vomiting, the vomitus at times containing small amounts of bright blood. There was the history of wine taken with his meals for many years; no other alcohol. The essential physical findings consisted of a firm, smooth liver edge felt about 7 cm. below the right costal margin and a spleen which was barely palpable. There was no icterus. There was no evidence of abnormal venous distention of his abdominal wall. A diagnosis of cirrhosis of the liver was made. An infra-red photograph of his abdomen showed more venous channels than would be expected in a normal individual. However, these were not as marked as those seen in other cases.

III. CASES WITH ENLARGED LIVERS FROM OTHER CAUSES.

CASE 7.—H. B., white male, aged 60, entered Rochester Municipal Hospital with the chief complaint of swelling of the legs of 3 weeks' duration. He had been dyspneic for several years. History of an attack of painless jaundice lasting about 2 weeks, 2½ years before admission. The stools had been tarry for several days. Physical examination revealed considerable edema of both ankles, a few coarse râles at the right lung base, slight enlargement of the heart to the left, a blood pressure of 170/80 and an enlargement of the liver, which at the time of admission extended about 5 cm. below the costal margin. The edge was firm and not tender. There was questionable evidence of ascites. No evidence of collateral venous circulation was seen. A diagnosis of cirrhosis of the liver and of hypertensive and arteriosclerotic heart disease was made. An infra-red photograph of the abdomen revealed no evidence of any increase in the collateral venous circulation. Routine treatment of congestive heart failure resulted in a definite diuresis with decrease in the size of the liver until the edge was no longer palpable. The patient's condition improved and he was discharged to go home with but slight evidence of congestive heart failure. No cause for the tarry stools was found.

CASE 8.—M. M., a single white woman, aged 56, was admitted to the Rochester Municipal Hospital because of weakness and loss of weight over a period of about 8 weeks. Very little else pertaining to her history could be obtained. On physical examination the abdomen was found to be greatly distended and there was a large, irregular, hard mass filling the epigastrium. The liver edge was easily felt just below the umbilicus. It was rough, moderately firm and slightly tender. Carcinoma of the stomach with metastases to the liver was the diagnosis made. No evidence of collateral circulation was apparent clinically. An infra-red photograph likewise showed nothing of this nature. She failed progressively and died. Autopsy examination showed a carcinoma of the ascending colon with metastases to the liver.

CASE 9.—G. E., a 65-year-old white man, had been admitted to the Strong Memorial Hospital 17 times over a period of 19 months for treatment of congestive heart failure. His liver had been enlarged throughout practically this entire period. No evidence of collateral circulation had

been apparent on his abdominal wall at any time. An infra-red photograph taken at a time when his liver reached almost to the level of the umbilicus showed no dilated veins. He is still returning at intervals for treatment.

Another case is reported to emphasize further the possible diagnostic value of this method.

CASE 10.—F. M., a white married woman, aged 34, entered the Rochester Municipal Hospital with the complaint of recurring attacks of right upper quadrant pain associated with jaundice over a period of 8 years. During this time she had passed tarry stools at times and gave the history of recent vomiting of bright blood. Eight years before this admission while convalescing in this hospital from scarlet fever, she developed upper abdominal pain and jaundice. Cholecystectomy was performed at this time. No stones were found in the gall bladder; the common duct was not explored because of operative difficulties. At the time of her last admission there was nothing found of any apparent significance on physical examination. No icterus was apparent, but a report of her icterus index from the laboratory was 20. The question arose as to whether she had cirrhosis of the liver or common-duct obstruction, possibly from a stone, as the cause of her complaints. No evidence of collateral circulation on her abdominal wall was apparent. An infra-red photograph also failed to show any such evidence. Because of the possibility that she had an obstruction of the common bile duct, an exploratory operation was performed which revealed absolutely nothing abnormal. The common duct was opened and probed. The liver appeared to be entirely normal in size and consistency. During her postoperative convalescence, the patient finally confessed that at least the majority of her complaints were feigned because of unpleasant home conditions.

Comment. From our small series of cases it would appear that infra-red photography offers a better means of demonstrating the collateral venous circulation in the abdominal wall than is afforded by any usual clinical method. In 4 cases in which a diagnosis of cirrhosis of the liver was made, photographic evidence of an increased venous pattern was found, though the diagnosis was confirmed at autopsy in only 1 case. Clinical evidence of collateral circulation was apparent in 2 of these cases, was questionable in another and was absent in the fourth. From this we are inclined to agree with Payne that the infra-red technique will demonstrate, in some cases, veins that are not visible to the naked eye. In every case in which an increased degree of venous distention was apparent both on the photograph and by direct inspection, it was by the former that the abnormality was better shown. In Case 2, this disparity was most marked; only moderate venous enlargement was apparent to the eye while the infra-red photograph showed this in striking degree. Case 5 is of interest in that cirrhosis of the liver was suggested by the history while there were no physical signs elicited to substantiate this diagnosis. However, an abdominal Roentgen ray suggested an enlarged spleen and a small liver and there was reason to believe that the spleen had been felt on one occasion. Interestingly enough in this case an infra-red photograph showed what was taken to be an abnormal degree of venous distention. In this type of case, if such a diagnosis is later established, it would

appear that infra-red photography, by demonstrating collateral circulation which was clinically not apparent, is of definite value.

Of a somewhat similar nature is Case 4. Here there was an indefinite history of abdominal discomfort and the only definite physical finding of a positive nature was an enlarged liver. The infra-red photograph showing an increased venous pattern suggests that this patient had some degree of portal obstruction. It is only by continued study of such cases as these last two that conclusions as to the significance of these findings will become apparent. This we intend to do.

In Case 10, negative findings with regard to evidence of collateral circulation both clinically and from an infra-red photograph may be of equal value with positive findings in other cases. Here, where there was the question of cirrhosis of the liver or common bile-duct obstruction, if the former could be excluded an exploratory operation would appear indicated, while if evidence pointing to cirrhosis were obtained the patient should be spared useless surgery. Such evidence we believe may be afforded by an infra-red photograph. In this particular case there was no evidence of portal obstruction at operation.

That liver enlargement *per se* does not produce signs of collateral circulation as judged by our standards, is clearly shown by the photographs of the abdomens of 2 patients with congestive heart failure and large livers, and another patient with a large liver resulting from carcinoma infiltration. No evidence of collateral circulation was apparent to the eye in any of these.

Occasionally, as in Case 7, it is necessary to attempt to decide whether an enlarged liver is due to congestive heart failure or to cirrhosis of the liver. In this case negative evidence from an infra-red photograph of the abdomen as well as from inspection, tended to rule out cirrhosis. The subsequent shrinkage of the liver coincident with a moderate diuresis during routine treatment for congestive heart failure seemed to exclude cirrhosis.

It is further conceivable that in cases of Banti's syndrome and other similar conditions where splenectomy is contemplated, information relative to the possibility of associated hepatic lesions, so frequently found, may be afforded by infra-red photography. If collateral circulation can be demonstrated on the abdominal wall damage of the liver sufficient to cause some degree of portal obstruction is probably indicated. Of course portal obstruction outside of the liver might well be expected to give the same findings with regard to venous distention. Obviously this knowledge would be of value in deciding on the probabilities of success from splenectomy.

Summary. Ten cases are presented in which there was evidence or suspicion of hepatic disorders. Clinical findings with regard to evidences for or against associated portal obstruction, as shown by the demonstration of collateral circulation on the abdominal wall,

are given. Comparison is made between the clinical findings and those obtained from ordinary and infra-red photographs of the abdomens of the patients presented. These data seem to indicate that infra-red photography may be of value in demonstrating degrees of collateral circulation which are not detected by usual clinical methods. At least it is an excellent means of recording abnormal degrees of superficial venous distention. Suggestions as to further application are made.

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STUDIES OF PERIPHERAL VASCULAR PHENOMENA.

IV. THE EFFECT OF ARTIFICIAL FEVER ON THE PULSE VOLUME CHANGES OF THE FINGER.

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SINCE the introduction of fever therapy in the treatment of disease there has been a renewed interest in the physiologic changes which occur during artificial fever. It is well known that in the fever of disease and in experimental and therapeutic fever, marked changes in the normal physiologic mechanisms occur, such as changes in the composition and volume of the blood, the cardiovascular system, and the irritability of the central nervous system. It is not within the scope of this paper to discuss these changes except as they are related to the problem at hand, namely, the study of peripheral vascular changes during artificial fever, and its effect upon the body in general.

Furthermore, we are aware of the fact that there are controversial points with regard to fever therapy such as: (1) The best methods of inducing artificial fever; (2) the degree of fever to be used; (3) the length of time the fever should be given.

This work has brought out many points of interest bearing upon these controversial points and we shall comment upon them briefly in the discussion.

Method. This study was made upon 2 individuals: (1) a normal control and, (2) a patient with rheumatoid arthritis. In addition clinical observations were made on a number of other patients during fever treatments.

In each experiment upon these individuals the blood pressure, respiration, heart rate and circulatory changes were measured at frequent intervals; *i. e.*, every 15 minutes to ½ hour. In addition, the rectal temperatures were recorded by a Brown Recording Resistance Thermometer. The circulatory changes were measured in one finger by a device previously described by Johnson[1]—an air conduction plethysmograph using colored alcohol for recording. Permanent calibrated records are made photographically on electrocardiograph paper, and estimation of finger volume change can accurately be measured to 0.002 cc. change. We interpret these changes as giving an index of the peripheral circulation (see Johnson,[1] Johnson, Scupham and Gilbert,[2] and Scupham and Johnson.[3])

In each experiment artificial fever to approximately 104.5° F. was induced and maintained for about 8 hours. The interval between each fever treatment depended upon the patient's clinical condition, but in most instances was about 1 week. One 8-hour control period was run during which no treatment was given.

Artificial fever was induced by the following methods: (1) Radiant heat—electric light cabinet; (2) radiant heat—infra-red; (3) hot water bath; (4) diathermy; (5) very high frequency oscillator; (6) foreign protein.

The fever was maintained during the course of the experiment by means of a zipper bag which prevents heat loss and can be removed rapidly in case of emergency, *i. e.*, if heat exhaustion or heat stroke occur. Means for giving emergency treatments were available at all times.

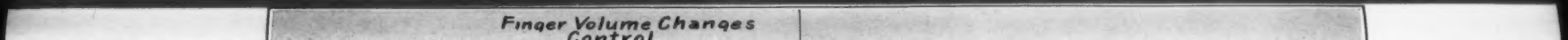
LEGENDS FOR FIGS. 1, 2, 3 AND 4.

FIG. 1.—Finger-volume changes during artificial fever periods. The record on the left is the control and the record on the right shows the effects of fever induced with a hot-water bath and maintained by prevention of heat loss. Note the minor variations in the control record as compared with the marked changes occurring during fever. Also note that the maximum excursions occurred at 103.8° F. while the maximum temperature used was 104.6° F. We interpret the increased volume changes of the finger as increased circulation.

FIG. 2.—The effects of artificial fever induced with external heat and maintained by the prevention of heat loss on the pulse, respiration, blood pressure and circulation. In the 1 case the radiant heat from the ordinary electric-light cabinet was used and in the other from the infra-red. Aside from minor variations the two records are not significantly different. In the experiment as shown by the record on the right the patient did not feel well, and we did not run the fever as high as in most experiments.

FIG. 3.—The results of artificial fever induced with foreign protein on the pulse, respiration, blood pressure and circulation. Note the primary vasoconstriction associated with the chill followed by a vasodilatation. The results of artificial fever on the peripheral circulation differ in this respect from those obtained with artificial fever induced with the application of external heat.

FIG. 4.—The effect of fever as induced by foreign protein upon the volume changes of the third finger of both hands 1 month after sympathectomy. It is noted that a striking change is obtained in the third finger of the control hand but virtually no change in the volume changes of the third finger of the sympathectomized hand. It is also to be noted that in the control hand, skin temperature and heart rate roughly parallel the volume changes of the finger. Very little change was observed in the sympathectomized hand. This indicates that vasodilatation of foreign-protein fever is chiefly of central origin.


Finger Volume Changes
Control

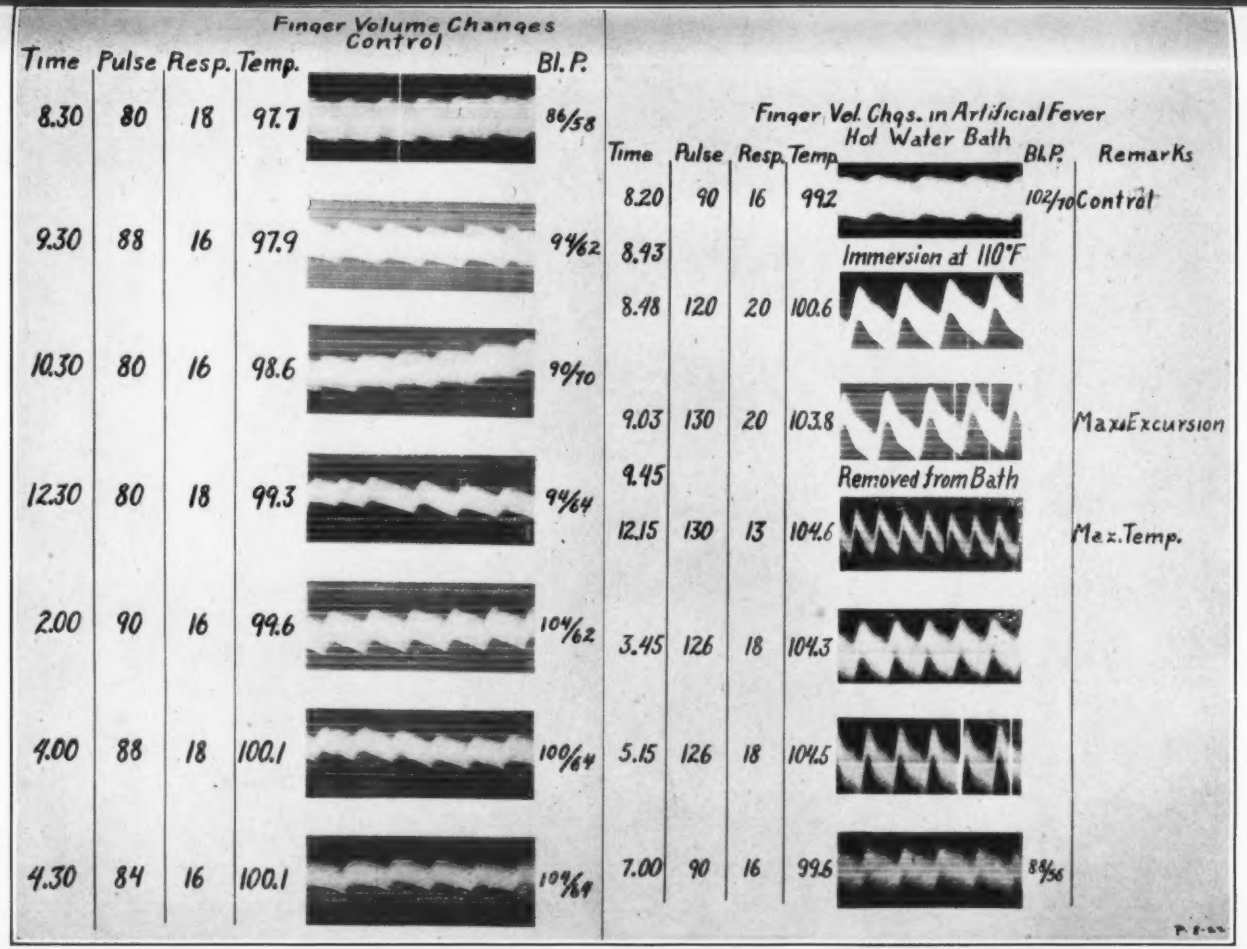
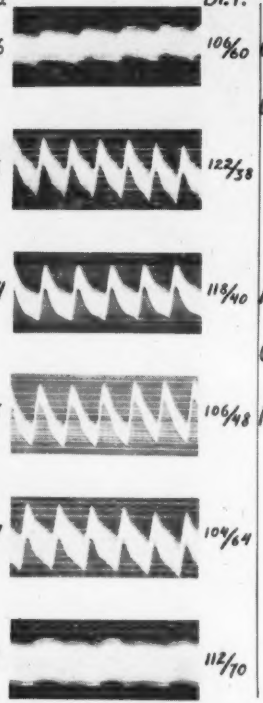

Finger Volume Changes
Control
Time
Pulse
Resp.
Temp.
Bl. P.
8.30
80
18
97.7
86/58
9.30
88
16
97.9
94/62
10.30
80
16
98.6
90/70
12.30
80
18
99.3
94/64
2.00
90
16
99.6
104/62
4.00
88
18
100.1
100/64
4.30
84
16
100.1
104/64
Finger Vel. Chgs. in Artificial Fever
Hot Water Bath
Time
Pulse
Resp.
Temp
Bl.P.
Remarks
8.20
90
16
99.2
102/70
Control
8.43
Immersion at 110°F
8.48
120
20
100.6
9.03
130
20
103.8
Max. Excursion
9.45
Removed from Bath
12.15
130
13
104.6
Max. Temp.
3.45
126
18
104.3
5.15
126
18
104.5
7.00
90
16
99.6
88/56

FIG. 1

UNIV. OF WISCH.

Finger Vol. Chgs. in Artificial Fever
Light Cabinet

Time	Pulse	Resp.	Temp.	Bl. P.	Remarks
8.20	70	16	98.6	110/60	Control
8.25					Current On
9.15	120	14	101.6	122/58	
9.45	124	14	104.4	118/40	Max. Temp.
9.45					Current Off
12.00	140	14	104.3	106/48	Max. Excursion
6.00	122	16	102.7	104/64	
7.45	82	16	99.1	112/70	



Finger Vol. Chgs. in Artificial Fever
Radiant Heat – Infra Red

Time	Pulse	Resp.	Temp.	Bl. P.	Remarks
8.30	78	16	99.4	94/52	Control
9.10					Current On
9.45					Current Off
10.00	108	20	101.5		Max. Excursion
10.30	110	20	102.4		Max. Temp
12.15	100	18	101.6		
2.15	100	16	102.1		
7.15	94	16	99.2	110/64	

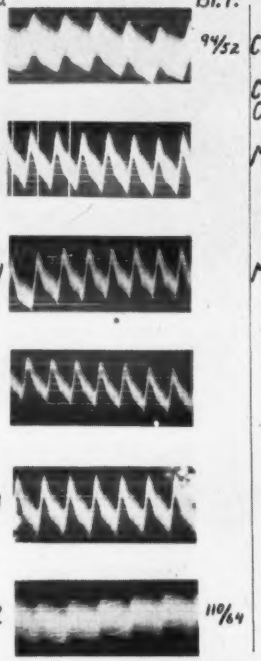


FIG. 2

FIG. 2

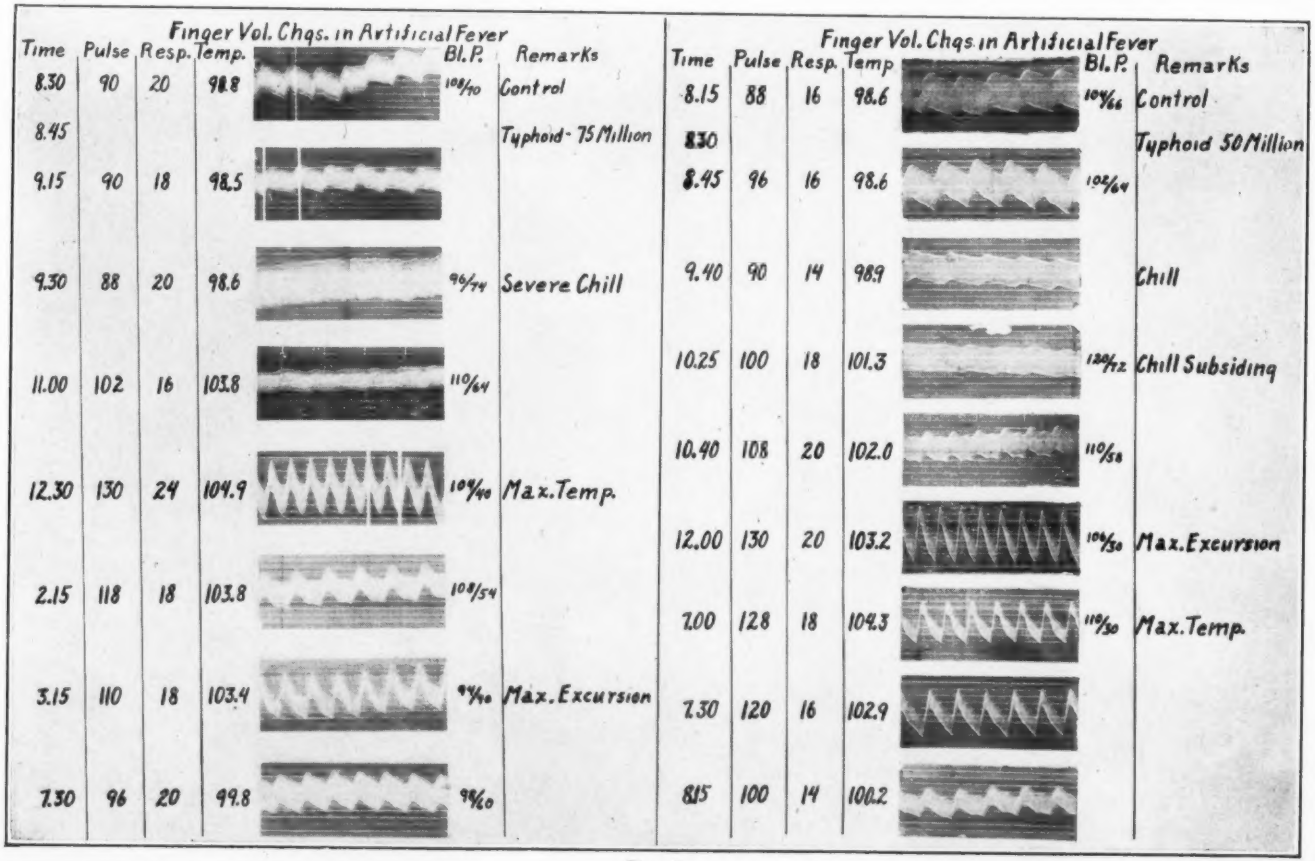

Finger Vol. Chgs. in Artificial Fever
Time Pulse Resp. Temp. Bl. P. Remarks
8.30 90 20 98.8 108/70 Control
8.45 Typhoid - 75 Million
9.15 90 18 98.5
9.30 88 20 98.6 96/74 Severe Chill
11.00 102 16 103.8 110/64
12.30 130 24 104.9 104/40 Max. Temp.
2.15 118 18 103.8 108/54
3.15 110 18 103.4 94/70 Max. Excursion
7.30 96 20 99.8 94/0
Finger Vol. Chgs in Artificial Fever
Time Pulse Resp. Temp Bl. P. Remarks
8.15 88 16 98.6 104/66 Control
8.30 Typhoid 50 Million
8.45 96 16 98.6 102/64
9.40 90 14 98.9 Chill
10.25 100 18 101.3 120/72 Chill Subsiding
10.40 108 20 102.0 110/58
12.00 130 20 103.2 104/50 Max. Excursion
7.00 128 18 104.3 110/50 Max. Temp.
7.30 120 16 102.9
8.15 100 14 100.2

FIG. 3

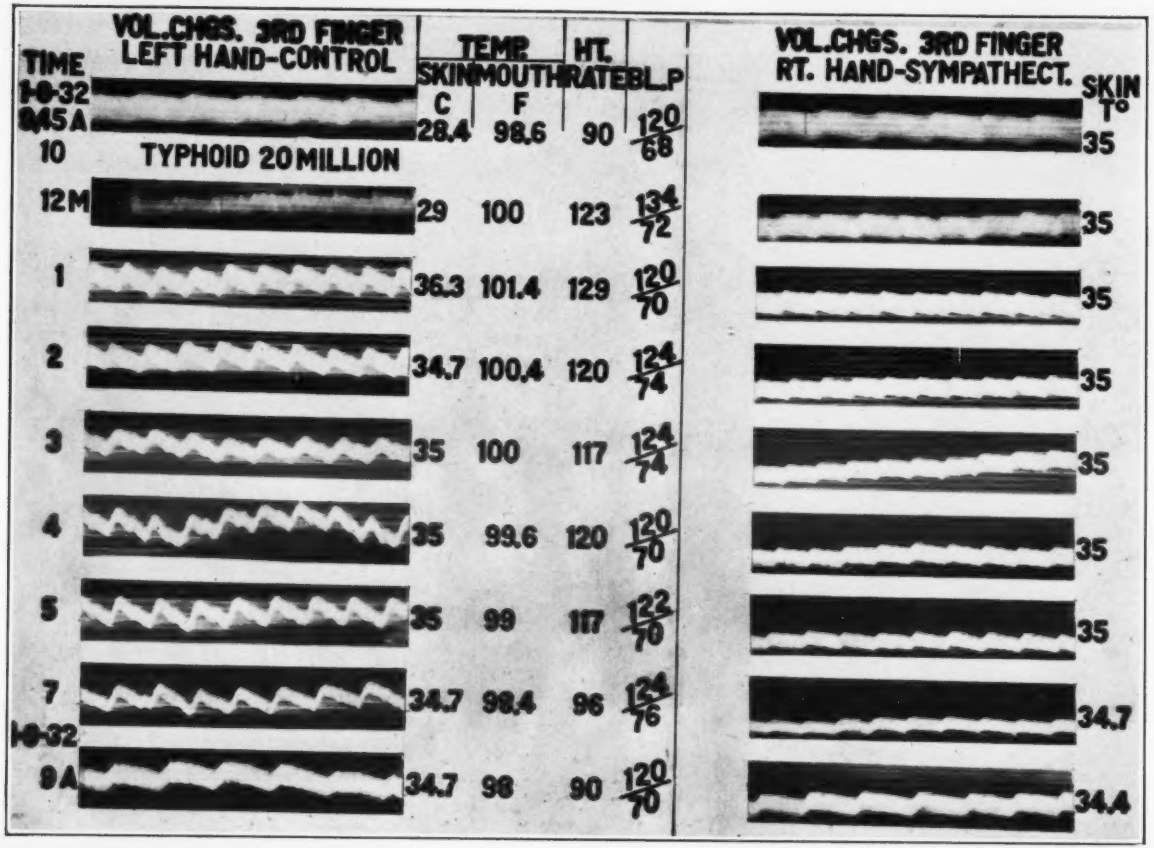

VOL.CHGS. 3RD FINGER
LEFT HAND-CONTROL
TEMP.
HT.
TIME
SKIN
MOUTH
RATE
BL.P
C
F
1-8-32
9:45 A
28.4
98.6
90
120/68
10
TYPHOID 20 MILLION
12 M
29
100
123
134/72
1
36.3
101.4
129
120/70
2
34.7
100.4
120
124/74
3
35
100
117
124/74
4
35
99.6
120
120/70
5
35
99
117
122/70
7
34.7
98.4
96
124/76
1-8-32
9 A
34.7
98
90
120/70
VOL.CHGS. 3RD FINGER
RT. HAND-SYMPATHECT.
SKIN T°
35
35
35
35
35
35
34.7
34.4

FIG. 4

FIG. 4

Results. The results may be tabulated as follows:

1. *Pulse-Volume Changes in the Finger.* *A.* There was a marked increase in the pulse-volume change in the finger with all types of artificial fever used except foreign protein in which a primary decrease occurred followed by an increase.

B. The maximum increase in pulse-volume change occurred at a temperature lower than the maximum used; *i. e.*, between 103 to 104° F.

C. The pulse-volume change fluctuated in amplitude after the maximum was reached.

D. The pulse-volume change remained above the control level throughout the experiment except with foreign protein as indicated above.

2. *Blood Pressure Changes.* As a rule, in normal individuals, there is a rise in the systolic pressure and a fall in the diastolic pressure during artificial fever, but in this patient there was not much change in the systolic pressure, but a rather marked fall in the diastolic pressure.

3. *Pulse Rate.* As a general rule this is increased during artificial fever.

4. *Respiration is also increased during fever.* As mentioned above the changes observed during the various types of artificial fever used, were essentially the same except with foreign protein and to save added illustrations we are only including typical records showing the phenomena indicated.

Figure 1*A* shows a control record taken for 8 hours. This has only minor fluctuations in the pulse-volume changes during the course of this period. In marked contrast to this, Figure 1*B* shows the tremendous increase in the pulse-volume changes when the body temperature is increased by immersion in hot water. These results of increased circulation from this procedure compares favorably with the results obtained in the arm by Hewlett, Van Zwaluwenburg and Marshall[4] with a different method. It will be seen that the maximum excursion occurred at 103.8° F. while the maximum temperature used was 104.6° F.

Figures 2*A* and 2*B* show two similar experiments except that the body was placed in a light cabinet. In the one experiment Figure 2*A* the ordinary radiant heat was used while in the other infra-red radiant heat was used. Both experiments showed marked increase in circulation.

Figure 3*A* shows the effect of artificial fever induced with foreign protein (typhoid injections) on the peripheral circulation. Both experiments show a primary vasoconstriction and in this way differs from the fever induced by other methods.

Figure 4 shows a similar experiment upon a patient with a unilateral cervical and upper dorsal ganglionectomy and ramisectomy. The control[4] side showed results similar to Figures 3*A* and 3*B* while

on the operated side no change was apparent. This patient showed a normal response to local heat on the control and operated side. For further details see Johnson, Scupham and Gilbert.[2]

Table 1 is a summary of the work showing that in general the maximum excursions occurred at temperature considerably lower than the maximum temperature used. This we interpret to mean that the maximum circulation occurs at a lower temperature than the maximum temperature used.

TABLE 1.—FINGER-VOLUME CHANGES WITH DIFFERENT TYPES OF ARTIFICIAL FEVER.

	Control.		Max amplit.		Max. temp. used.		Final record.	
	Amplit.	Temp.	Amplit.	Temp.	Amplit.	Temp.	Amplit.	Temp.
Radiant heat, electric light cabinet	0.013	99.5	0.045	103.4	0.030	104.6	0.022	99.4
Radiant heat, electric light cabinet	0.010	98.6	0.052	104.3	0.038	104.4	0.009	99.1
Radiant heat, infra-red	0.027	99.4	0.052	102.1	0.047	102.4	0.010	99.2
Radiant heat, infra-red	0.010	98.2	0.080	103.4	0.071	104.4	0.026	99.0
Hot water bath	0.010	99.2	0.060	103.8	0.048	104.6	0.020	99.6
Diathermy	0.013	98.0	0.054	103.4	0.032	104.7	0.043	102.6
High frequency oscillator	0.013	98.2	0.070	104.2	0.055	104.7	0.029	99.7
Foreign protein	0.013	98.6	0.052	103.7	0.042	104.4	0.015	99.5
Foreign protein	0.012	98.8	0.043	104.9	0.043	104.9	0.018	99.8
Control	0.008	97.7	0.016	99.6	0.010	100.1	0.010	100.1

The amplitude is measured in cubic centimeter volume change of the finger and the temperature is the rectal temperature.

This table illustrates that in the majority of the experiments that the maximum finger-volume changes occured at a temperature considerably below the maximum temperature used. We interpret this as meaning that the maximum circulatory changes occur at the lower temperatures, and that there is an optimum temperature for the maximum circulatory change.

Discussion. These results show an increased pulse-volume change with all types of the artificial fever used except foreign protein which gave a primary decrease of the pulse-volume change which was associated with the chill.

We interpret the increased pulse-volume change as increased circulation as a result of the vasodilatation and probably increase cardiac output. As mentioned in a previous report we indicated that the interpretation of the pulse-volume change is open to some question and also that the same factors which maintain blood pressure in addition to the resistance of the soft tissues in question as the important factors in determining the extent of the excursion. It might be possible to have an increased circulation without increased pulsation but not possible to have an increased pulsation without increased circulation. In these experiments the excursion was markedly increased during the course of the fever except in those experiments where foreign protein was used to promote the fever.

The effect of artificial fever upon the peripheral circulation when induced by general heat with prevention of heat loss was about the same with all of the methods used (Table 1). The finger volume change increased from about 0.01 cc. control to 0.06 to 0.08 cc. The striking feature is that the maximum circulatory response occurred at temperatures considerably lower than the maximum used. Furthermore, the amplitude of the excursions measuring the circulatory response showed marked variations as the temperature was maintained which we interpreted as due to instability of the vasomotor system, and instability of the heat regulating mechanism which is intimately associated with the vasomotor system. These results indicate that there may be an optimum temperature at which a maximum circulatory response occurs. This suggests that high therapeutic fevers up to 106° as often used are too high unless factors other than circulation play a rôle and are only brought out by fevers above the optimum.

That factors other than circulation are important in therapeutic fever are indicated by another very interesting observation in this study:

The circulatory response to artificial fever induced with foreign protein differed from those obtained with artificial fever induced by external heat. Foreign protein uniformly in 5 patients gave a primary vasoconstriction associated with the chill and followed by a vasodilatation. The vasodilatation was never as great as that produced by the other methods unless heat loss was prevented by insulating the body and the fever maintained. Clinically good results are obtained with foreign protein therapy in spite of the fact that the peripheral circulatory response is not as great with fever induced by other methods.

The fundamental difference in the results of the two types of artificial fever, *i. e.*, the foreign protein fever and that produced by external heat, is that the vasoconstriction and vasodilatation of foreign protein fever is probably of central origin, while the vasodilatation with fevers produced by the other means is chiefly of peripheral origin. For further details see the article by Johnson, Scupham and Gilbert.[2]

In this work a number of clinical observations were made which are worthy of mention:

Artificial fever induced by external heat is dangerous unless proper precautions are taken and even then some patients do not tolerate fever well, particularly those with impairment of the cardiovascular system.

First, one should have proper equipment. A recording thermometer should be used so that an accurate observation of the temperature can be had at all times. A physician should be present at all times and means for emergency treatment of heat exhaustion should be available.

The ability to tolerate this type of artificial fever seems to be related to the cardiovascular reserve. Some patients under mild fever will develop symptoms of cardiac insufficiency such as dyspnea, cyanosis and the respirations will be markedly increased. In 1 case auricular fibrillation started at 102° (rectal temperature). Another patient vomited for a week after fever of 101° for 2 hours while a third patient persistently had convulsions with temperatures around 104°. These illustrations merely show that: (1) arbitrary standards of treatment cannot be fixed for this type of therapy and, (2) the patient requires constant attention from a physician to minimize the danger.

The question of how long the fever should be maintained is debatable. We feel that it should not be run to the point of exhaustion. This will vary from patient to patient and treatment to treatment.

Regarding the best method of inducing artificial fever from external heat we can only say that in view of the danger attended with this type of therapy that the safest method should be used. This is probably the ordinary electric light cabinet. The most dangerous method is probably the hot water bath.

We are in agreement with Simpson[5] that the possibility of doing harm with unskilled workers or trying to carry out this treatment with inadequate equipment is perhaps greater than the possibility of doing good. We also feel that more fundamental work dealing with physiology of fever is essential before this procedure can be carried intelligently.

Summary and Conclusion. The effects of artificial fever upon the peripheral circulation have been presented and may be briefly summarized as follows:

1. There was a marked increase in the pulse-volume changes of the fingers with all types of artificial fever used, except foreign protein which gave a primary decrease associated with the chill, but followed by an increased circulation.

2. The vasodilatation of foreign protein fever is probably of central origin while the vasodilatation with artificial fever induced by external heat and preventing heat loss is chiefly of peripheral origin.

3. The maximum increased circulation from artificial fever occurred in general at temperatures between 103 and 104° F. while the maximum temperature used was 104.5°. This suggests that there is an optimum temperature at which peripheral circulation reaches a maximum.

4. Artificial fever from external heat and prevention of heat loss is dangerous and should not be used unless adequate facilities are available and should not be left in the hands of a technician.

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METABOLIC RATES IN THERAPEUTIC FEVER.

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The parallelism between fever and variations in the metabolic rate is well known. The major part of the work in this field has been done upon patients with febrile diseases such as typhoid, malaria, tuberculosis, erysipelas, etc., and upon patients in whom temperature rise has been produced by means of intravenous proteose and typhoid vaccine.[1–5] But little work has been done on fever produced by the more recent physical methods. Neymann and Osborne[6] found an average rise of 7% in the metabolic rate for each degree fever (F) in patients in whom body temperature was raised by means of diathermy current. Nasset and coworkers[7,8] induced fever in anesthetized dogs by means of diathermy and found an average increase of about 12.5% in the metabolic rate for each degree of temperature (C) rise. In one dog an increase of 313% above basal conditions occurred. No quantitative relationship was found between rise in body temperature and increase in the metabolic rate. The use in this clinic of several methods for the induction of fever in the treatment of central nervous system syphilis permitted a study and comparison of the increases in the metabolic rate obtained by these different methods.

Subjects. Seven male patients were selected from a large group who were given fever therapy. These patients varied from 32 to 46 years; 5 (F. K., A. J., S. M., J. W., J. H.) were diagnosed by clinical and laboratory procedures as general paresis; M. J. as tabes dorsalis with gastric crisis; W. S. as meningovascular neurosyphilis; F. K. was found to have a consistently low basal metabolic rate on numerous repeated tests, but myxedema was not present. All patients were hospitalized during fever therapy, and were given the customary mixed hospital diet.

Methods. Fever was induced by 5 different methods: 1, Diathermy current; 2, electric light cabinet and hot moist air; 3, a method combining (1) and (2); 4, electric blanket; 5, mixed typhoid vaccine intravenously.

In 6 patients fever was induced only by means of the combined method of diathermy current, electric cabinet and hot moist air. Body temperature was raised to 104° to 105° F. in from 60 to 90 minutes and then allowed to fall. In 1 patient, F. K., body temperature was prolonged by this method at arbitrary levels from 1 to 3 hours during which a series of metabolism determinations were obtained. In addition, fever was induced in patient, F. K., by all 5 methods allowing for a comparison of the metabolic rates in fever induced by the different methods in the same individual.

The diathermy machine used is that of the General Electric, Victor type. Insulation was obtained by means of a celotex cabinet, containing eight 60 Watt electric lamps, and by means of rubber and woolen blankets. The latter type of insulation is more uncomfortable than the former. With the electric cabinet insulation the heat given off by the lights is considerable and both dry and wet bulb temperatures rise rapidly, reaching a level of about 115° F. and 100° F., respectively, in an hour. In addition air blankets of different dry and wet bulb temperatures are present as one proceeds from body level to the top (19 inches above) of the insulating cabinet.

Two different sets of electrodes were used for diathermy treatment: 1, fenestrated electrodes applied to chest, abdomen and back and kept in place by means of a canvas jacket and 2, segmented bracelet electrodes encircling both thighs, arms and waist.

The electric blanket is merely an enlarged electric heating pad. The patient, except for the head, is covered with rubber and insulating blankets, and then enveloped in a large electric mesh blanket. The blanket temperature fluctuates from about 115° to 130° F.

Typhoid vaccine fever was induced in patient, F. K., by the intravenous injection of 150 million mixed organisms.

Rectal temperatures were used and were obtained by means of a self-recording motor-driven temperature unit. Where temperature changes occurred during the metabolism test an average reading was taken.

A portable Benedict-Roth metabolism machine was used to determine the metabolic rate over 6- or 7-minute intervals. The DuBois standards as modified by Boothby and Sandiford were followed in the calculation of the results. The initial weight of the patient was taken even though there occurred, as a rule, a loss of from 1 to 5 pounds in weight during treatment, the loss in weight depending upon the duration of treatment and the fluid intake. The changes in weight involved a maximum variation of ± 2.5% in the results obtained.

Treatment was usually given every second or third day. On the morning of treatment, a light breakfast was allowed at 6.30 A.M. to 6 patients. This light breakfast consisted largely of carbohydrates, some protein, and very little fat. The seventh patient, F. K., was able to undergo all fever treatment under basal conditions. At 8.00 A. M. the patient was weighed and then allowed a rest period in bed of from 45 to 75 minutes. An initial metabolic rate was then determined and in the case of patient F. K., repeated. Fever treatment was then started.

Results and Discussion. The initial metabolic rates obtained on each patient before the start of fever therapy on each treatment day revealed fluctuations of from 15% to 35% (Chart I). In 4 of the 7 patients greater variations than the usually accepted ±10% for one's basal metabolism were present and may well be due to the effect of the early morning meal which though restricted was not

uniform. No attempt was made to estimate quantitatively the intake of food, but since metabolic determinations were not made for from 2 to 2½ hours after the light breakfast allowed, the effect of food was probably slight and became less so as body temperature was rising. Soderström and coworkers[9] have shown that a light breakfast of 222 calories consisting of one slice of bread (30 gm.), 60 cc. milk, and 8 gm. of butter (a breakfast consisting of 4.7 gm. protein, 9 of fat, and 28.9 of carbohydrate) increased heat production only 7%, 2%, and 2%, the first, second and third hour respectively after ingestion. The initial metabolic rates of patient, A. J., who was allowed an early breakfast, and who could best tolerate fever therapy showed the least variation (15%). The greatest fluctuation in the initial metabolic rates occurred in patients, S. M., and M. J., who were the most uncomfortable and restless during fever therapy. Patient F. K., under basal conditions, showed variations of 20% in the basal metabolic rate on 47 determinations. When the rates of this patient were taken chronologically, it was seen that repeated fever therapy over a period of 7 months had no residual effect on the basal metabolic rate.

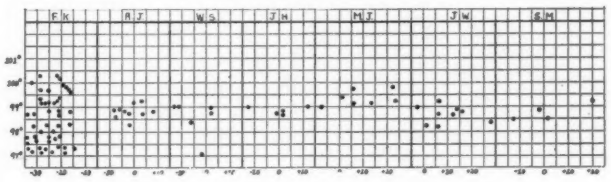

CHART I.—Initial metabolic rates.

The metabolic rates of the 7 patients during fever induced by diathermy current combined with the electric cabinet and hot moist air are seen in Chart II. As the body temperature was rising rapidly 140 determinations were made and 180 as the body temperature fell after the insulating electric cabinet had been removed. The metabolic rates tended to increase as the body temperature was raised but variations of a marked degree occurred at different temperature levels, whether the body temperature was rising or falling. These variations, as much as 70%, are much more marked when the results of all the experiments are grouped together than when the results of each patient are considered separately. The metabolic rates of the 7 patients during this type of induced fever revealed an average increase of from 5 to 14% for each degree rise of body temperature. Repeated experiments revealed also fluctuations for each patient for similar temperature levels so that the rise in metabolic rate was not absolutely uniform as body temperature increased. The degree of fluctuation appeared to depend to a large extent upon the amount of discomfort present during fever treatment as revealed

especially by hyperpnea and restlessness. Patients, S. M., and M. J., in whom restlessness and hyperpnea were most marked, showed the greatest average increase in metabolic rate, 10% and 14% respectively, for each degree of temperature rise. Patient, A. J., who experienced very little discomfort during fever therapy showed an average increase of only 5% for each degree temperature rise. The effect of hyperpnea and discomfort during fever upon the metabolic rate has already been pointed out by various observers.[10,11] The removal of the insulating cabinet when body temperature had reached its desired height and the exposure of the patient to room

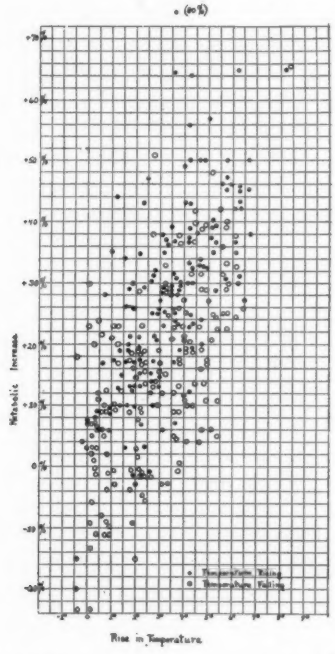

CHART II.—Increase in metabolic rate in diathermy fever.

temperature and humidity was accompanied in most cases by a rather rapid and steep fall in metabolic rate. This occurred whether body temperature remained at the same level, fell, or even continued to rise. Following this preliminary drop, the metabolism tended to fall quite slowly. At times the drop following uncovering of the patient would be so steep that the metabolic rates obtained thereafter even though fever was still present, would not vary much from that obtained at the start of the experiment. As a rule, however, with uncovering, the metabolic rate would fall to a level above that obtained before fever was induced and then fluctuate within narrow limits about this level even though the temperature fell as much as

4° to 5° F. The final metabolic rate obtained at the end of each experiment, when body temperature was nearly or the same as at the start of the experiment, also showed variations from the initial metabolic rates even as much as 30% (Chart II).

Barr and DuBois,[2] following observations on patients with malaria, have stated that with an increased temperature increased heat production occurs, and that the elimination of heat by means of the expired air and evaporation of sweat from the body surface

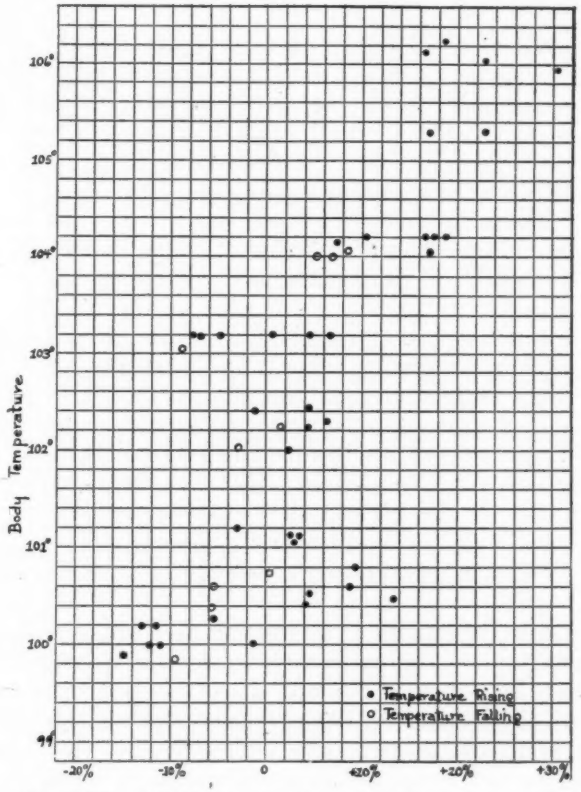

CHART III.—Metabolic rates at sustained temperature levels.

remains fairly constant. With a fall from a higher to a lower body temperature heat elimination through these channels is increased considerably, and heat production tends to fall to a low level slightly above normal. During the fall in body temperature there is no marked decrease in heat production, but a gradual lowering of production to a normal level. According to these observers no mechanism is present by which heat production can be lowered abruptly. The rather rapid and steep drop in metabolic rate occurring after the removal of the insulating box and its hot air blanket

whether body temperature fell, rose, or remained at the same level in the experiments reported above must be attributed not only to the above described mechanism of temperature fall but, also, to the removal of the hot humid air blanket which by itself is capable of producing changes in the metabolic rate whether body temperature is increased or not.[12,13] The increase in metabolic rate caused by the air blanket is due (*a*) to the heating of the peripheral body tissues to a temperature above that recorded rectally and (*b*) to the disturbing effects of a variable degree produced in each individual patient.

When fever was induced in patient F. K. by the combined method of diathermy, cabinet, and moist air, and body temperature prolonged at arbitrary levels, the metabolic rates obtained at these different levels showed a rather suggestive linear relationship to the temperature (Chart III). In these experiments, also, a lower metabolic rate was obtained as a rule when body temperature fell during the determination than when it was rising. The determinations in these experiments were made after the diathermy current had been turned off, contrary to the method used for the determinations shown in Chart II.

It is our experience that metabolic rates obtained as the body temperature rises are usually higher than when obtained at the same or even higher levels after the diathermy current has been turned off. Occasionally the metabolic rate would show a fairly marked drop after body temperature had been maintained at the same level for a few hours. When hyperpnea is present as body temperature is rising rapidly, the turning off of the diathermy current usually results in greater comfort and the disappearance of hyperpnea even though the body temperature remains at the same level or continues to rise.

The question then arises as to whether diathermy current *per se* has any effect upon the basal metabolism and is responsible for some increase in the metabolic rate when this type of fever induction is used. Nasset[8] altered the kilocycle value of the diathermy current used in dog experiments and concluded that diathermy current *per se* had no specific effect upon the metabolic rate. Repeated metabolism determinations on patient F. K. (Table 1) following short periods of diathermy current, revealed no appreciable effect of diathermy current upon the basal metabolic rate when no change or even very little change in body temperature occurred. Alterations of current frequency at high temperature levels also caused no appreciable changes in the metabolic rate. The differences in the metabolic rate obtained at an increased body temperature before and after the turning off of the diathermy current is due to the disappearance of the hyperpnea and discomfort of the patient and not to any specific effect of diathermy current upon the basal metabolic rate. Similar conclusions were drawn

by Nasset and coworkers.[7] However, the drop in the metabolic rate in anesthetized dogs at increased temperature levels when the diathermy current was turned off, even though body temperature continued to rise, could not, according to these observers, be accounted for by diminished respiratory activity alone.

TABLE 1.—THE EFFECT OF DIATHERMY CURRENT PER SE ON THE BASAL METABOLIC RATE.

Time.	Pulse.	Body temperature, ° F.	Box temperature, ° F.	Comment.	Metabolic rate.
9:25	74	97.4–97.2	79	...	−19.8%
9:31	72	97.2–97.2	79	...	−33.6%
9:59	..	...	..	Current on 2000 M.A.	
9:59	84	97.2–97.3	79	...	−31.1%
10:06	84	97.3–97.4	79	...	−33.9%
10:12	..	...	..	Current off	
10:33	76	97.3–97.4	80	...	−32.7%
10:38	76	97.4–97.3	80	...	−32.7%
11:12	..	...	..	Current on	
11:12	80	97.2–97.3	82	...	−23.5%
11:18	80	97.3–97.6	82	...	−27.6%
11:26	..	...	..	Current off	
11:55	72	97.6–97.6	84	...	−23.8%
12:02	..	...	..	Sparksgaps opened wide—2400 M.A.	
12:02	80	97.6–98.2	84	Slight diaphoresis	−25.3%

In Charts IV, *A* and *B* are shown the metabolic curves obtained on patient F. K. as body temperature was rising and falling in fever induced by the following five methods: 1, Diathermy current; 2, electric cabinet and hot moist air; 3, a method combining 1 and 2; 4, electric blanket; 5, typhoid vaccine.

TABLE 2.—THE PERCENTAGE RISE OF METABOLIC RATE FOR EACH DEGREE RISE OF TEMPERATURE IN DIFFERENT FORMS OF THERAPEUTIC FEVER.

Typhoid vaccine	9.3%
Electric blanket	7.9%
Diathermy, cabinet and hot moist air—Exp. I	7.7%
Exp. II	7.7%
Electric cabinet and hot moist air	6.9%
Diathermy—Exp. I	3.9%
Exp. II	2.4%

A rather striking parallelism is seen in all methods of fever induction except when diathermy current alone is used. (The marked increase in metabolic rate in this patient during the typhoid vaccine chill, plus 170%, is not included.) The average increase in metabolic rate for each degree of temperature rise (Table 2) varied from 2.4% and 3.9% for fever induced by diathermy current alone to 9.3% for typhoid vaccine fever. The results obtained in these different methods of fever induction agree quite well with the accepted rise of 7.2% for each degree of body fever[14] except for diathermy current alone. The small increase in the latter type of fever may be due (*a*) to the absence of any protein destruction in fever induced by diathermy alone and (*b*) to the absence of the hot moist air blanket.

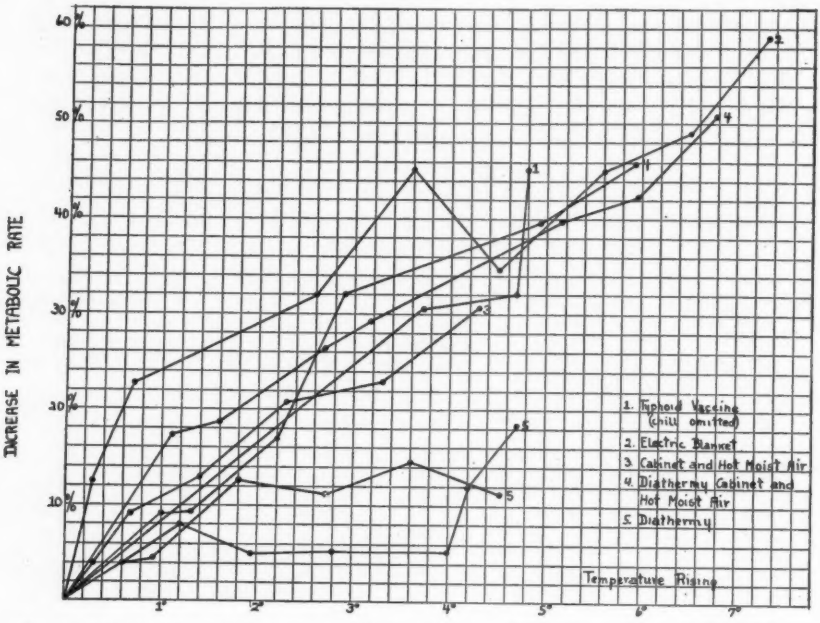

CHART IV *A*.—Comparison of metabolic rates in different modes of therapeutic fever.

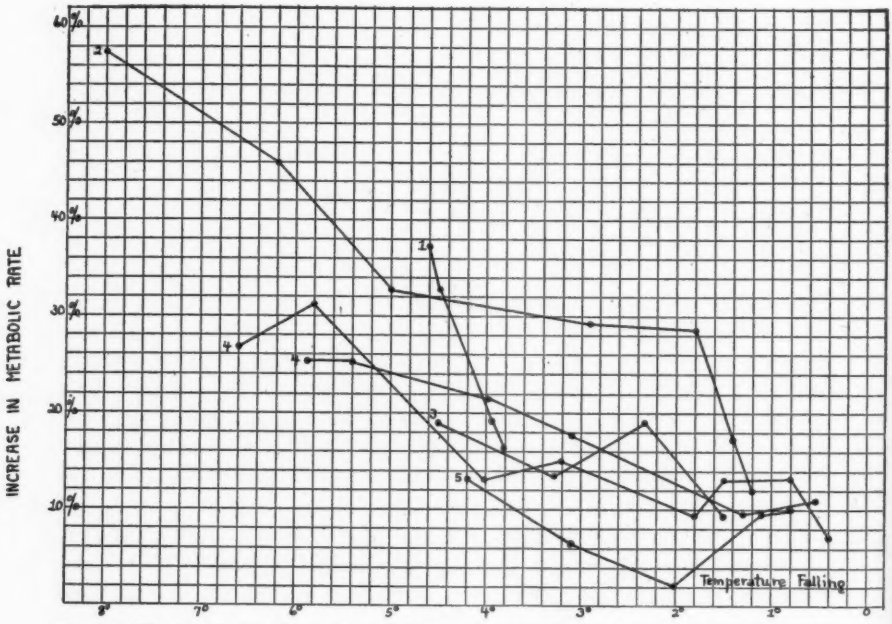

CHART IV *B*.—Comparison of metabolic rates in different modes of therapeutic fever. (See Chart IV *A*.)

The rapidity of body temperature rise did not appear to play any part in the results obtained in these five different methods (Table 3), contrary to the belief of some that higher metabolic rates are obtained in acute fevers than in chronic ones.[10,11] Nasset and coworkers[7] felt that the rate of increase in body temperature was an important factor in the high metabolism results obtained by them on dogs in whom body temperature was raised by diathermy. Fever induction in patient F. K. by means of diathermy current combined with the electric cabinet and hot moist air required an average of 11 minutes for each degree of body temperature rise. In fever induced by the electric cabinet and hot moist air, an average of 63 minutes was required for each degree of temperature rise. In spite of this marked difference in time interval the increase in metabolic rate for each degree of body temperature in both instances was about the same, 7.7% and 6.9% respectively (Table 2).

TABLE 3.—A COMPARISON OF THE RATE OF RISE OF BODY TEMPERATURE IN THERAPEUTIC FEVER.

	Temperature Range.	Minutes per degree rise.
Diathermy, cabinet and hot moist air	99.5–105.7	11
	98.2–105.3	11
Typhoid vaccine	99.0–103.8	30
Electric blanket	97.8–105.4	33
Diathermy current	99.2–104.0	35
	97.2–101.8	39
Electric cabinet and hot moist air	99.6–104.0	63

A rather rapid and fairly marked drop in the metabolic rate occurred when patient F. K. was uncovered and body temperature allowed to fall in fever induced by the cabinet and hot moist air, and by the combined method of cabinet, moist air and diathermy. A similar but less marked fall occurred in fever induced by the electric blanket and typhoid vaccine. In fever induced by diathermy current alone, the metabolic rate was approximately the same when body temperature was rising and falling. The drop in metabolic rate with uncovering of the patient was most marked in those methods in which hot, moist air was a factor in raising body temperature.

Summary. 1. Metabolic rates were determined on 7 patients with neurosyphilis in whom fever was induced by artificial means. In 6 patients in whom fever was induced by the combined method of diathermy current, electric cabinet and hot moist air, determinations were started about 2½ hours after a light breakfast. In the seventh patient in whom fever was induced by 5 different methods: *a*, Diathermy current; *b*, electric cabinet and hot moist air; *c*, a method combining (*a*) and (*b*); *d*, electric blanket; *e*, mixed typhoid vaccine; all determinations were made under basal conditions.

2. An increase in the metabolic rate occurred when fever was induced by the combined method of diathermy current, electric light cabinet and hot moist air. Though a rather suggestive linear

relationship was present, fluctuations of a fairly marked degree occurred at different temperature levels when the group is taken as a whole. This may be due to individual variations in the degree of discomfort manifesting itself especially by hyperpnea, the metabolic rates at higher levels paralleling, as a rule, the amount of hyperpnea present.

Repeated metabolic rates obtained on 1 patient under basal conditions in a series of experiments during which body temperature was raised by similar methods and maintained at different levels from 1 to 3 hours revealed a fairly uniform increase in body metabolism for each degree of temperature rise.

3. The removal of the insulating hot, moist air blanket when body temperature had reached its desired height was followed in nearly all cases by a rather steep fall in metabolic rate, whether body temperature remained at the same level, fell or even rose.

4. Metabolic rates for similar temperature levels were higher when the temperature was rising than when falling.

5. Diathermy current *per se* over short time intervals had no specific effect upon the basal metabolic rate provided no rise in body temperature occurred. Alteration of the frequency of the diathermy current at increased temperature levels also caused no appreciable change in the metabolic rate.

6. The increases in metabolic rate obtained on the 1 patient in whom temperature rise was induced by the 5 different methods enumerated above showed a rather striking parallelism and did not differ much from the accepted rise of 7.2% for each degree Fahrenheit except in fever induced by diathermy current alone. In the latter the average rise in metabolic rate was 2.4% and 3.9% for each degree fever. The rapidity of rise in body temperature played no part in the results obtained.

7. Repeated fever treatment of 1 patient over a period of 7 months had no residual effect upon the basal metabolic rate.

The writer gratefully acknowledges the many helpful suggestions and encouragement of Dr. Harry C. Solomon.

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A STUDY OF THE COAGULATION DEFECT IN HEMOPHILIA AND IN JAUNDICE.*

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Progress in the management of hemorrhage in hemophilia and in certain types of obstructive jaundice has been much impeded by the lack of a practical concept of blood clotting. A distinct need exists for a simple theory which may serve as a guide in the clinical study of disturbances in the clotting function of the blood. Recently Wöhlisch[1] in a thorough and critical review of the coagulation of blood, constructed a theory which incorporates the essential ideas of Bordet,[2] Morawitz,[3] and others. According to this concept clotting proceeds in two phases:

I. Prothrombin + thromboplastin + calcium = thrombin
II. Fibrinogen + thrombin = fibrin

Thus, only 4 constituents are essential for clotting: prothrombin, thromboplastin, calcium, and fibrinogen. By the interaction of the

* This work was presented before the Twenty-ninth meeting of the American Society of Biologic Chemists at Detroit, April, 1935. It was supported by the Blossom Fund.

first three components, thrombin is formed, and this substance has the power to convert soluble fibrinogen into insoluble fibrin. If this simple concept of blood clotting is correct and sufficiently comprehensive, any disturbances in coagulation should be traceable to a qualitative or quantitative alteration in one of these essential components. In this study these 4 substances were carefully considered in an effort to find and to develop satisfactory methods for their estimation or quantitative determination. From a review of the literature, it became apparent that fibrinogen and calcium were probably rarely responsible for disturbances in blood clotting and therefore required little consideration other than a brief summary of their relation to clotting.

Fibrinogen. The concentration of fibrinogen in plasma varies normally from 0.3 to 0.75%, but this wide range has no demonstrable effect on clotting time. We have even found that adding purified fibrinogen to plasma does not alter the speed of clotting. It seems fairly certain that fibrinogen plays an entirely passive rôle, and that the rate of clotting depends primarily on the concentration of thrombin. Nevertheless, it is obvious that in the total absence of fibrinogen, no clotting can occur, and interestingly, 2 such cases have been reported in which fatal hemorrhage had to be attributed to a lack of fibrinogen in the blood.[4,5] This condition Wöhlisch[1] has named pseudohemophilia. It can be reproduced in animals as illustrated by the following experiment:

A freshly prepared and filtered saline extract of rabbit brain (20 cc.) was injected intravenously into a dog. A severe reaction occurred immediately, respirations became shallow, and a nystagmus developed. The fibrinogen which was 0.44% before the injection dropped to 0.09 in 5 minutes and to a mere trace 30 minutes after the injection. The dog was killed 1 hour later and autopsied. No definite intravascular clotting could be found, but there was a relatively small pulmonary infarct and also a small mesenteric infarct.

While fibrinogen does not influence the clotting time, it is conceivable that if its concentration is too low, a fragile and poorly adhering clot will form. In hemophilia, however, a normal fibrinogen concentration has been found by all investigators.[6,7,8] In obstructive jaundice the literature is more conflicting. The work of Doyon,[9] Whipple and Hurwitz[10] Foster and Whipple[11] and others show that liver damage can markedly reduce the blood fibrinogen. Recently, however, Linton[12] studied a series of obstructive jaundice cases, and found an elevation of fibrinogen even in those patients that died from hemorrhage. We have obtained essentially similar results. It seems fairly improbable, therefore, that fibrinogen deficiency can be the causative factor for the hemorrhagic diathesis.

Calcium. Contrary to the widely accepted view that ionized calcium of the blood influences the rate of clotting, it seems more

likely that it is only the organically combined calcium which is directly essential for the formation of thrombin. Scott and Chamberlain[13] have demonstrated that the quantitative removal of ionized blood calcium with oxalate will not prevent clotting; and they as well as Vines,[14] and Steward and Percival[15] have found that it requires 3 times the theoretical amount of oxalate before clotting is completely inhibited, which suggests that the organically bound calcium must be precipitated before the clotting process is stopped. Eagle[16] in a recent paper discussed the possibilities that thrombin may be a calcium-containing compound. Since these same considerations may be applied to prothrombin, it is likewise conceivable that in the latter, calcium may be an essential part of the molecule and that therefore in the conversion of prothrombin to thrombin, inorganic calcium perhaps plays no direct rôle. Ionized calcium is however a dominant factor in platelet lysis, as Ferguson[17] has convincingly demonstrated in a recent work, thus confirming the observations of the older investigators. The question why calcium only becomes effective in shed blood still remains unanswered. It is doubtful whether clinically even marked changes in the concentration of inorganic blood calcium have any significant influence on the clotting time. No hemorrhagic diathesis has been observed in the extreme hypocalcemia of parathyroid deficiency, nor has intravascular clotting been reported in cases of hyperparathyroidism in which hypercalcemia of long duration often was present. Experimentally, Ravdin, Riegel, and Morrison[18] could demonstrate no change in the coagulation time of blood after inducing a hypocalcemia in dogs by parathyroidectomy, nor by bringing about an elevation of blood calcium with parathormone. In hemophilia the concentration of calcium in blood is normal,[19,20,21] and in obstructive jaundice, even in severe hemorrhagic cases, no significant change in blood calcium is found. Wangensteen[22] who has carefully reviewed the literature concluded that a deficiency of calcium has not been adequately demonstrated in any hemorrhagic disease. Ravdin and his coworkers were unable to reduce the clotting time of normal and of jaundiced dogs by intravenous calcium injections. It is probable that any beneficial effect obtained by calcium administration may be due to its therapeutic action on liver function rather than on any direct influence on clotting.

Since neither fibrinogen nor calcium seem to be important factors in the hemorrhage seen in hemophilia or obstructive jaundice, attention must be centered on prothrombin and thromboplastin. Unfortunately no generally accepted methods for studying these two agents are available; in fact, even their nature is still a subject of controversy. The first task that had to be undertaken was the development of a method for estimating prothrombin, and the second, the preparation of a stable and active thromboplastin.

The method developed for the estimation of prothrombin depends

on the conversion of this substance to thrombin, and determining the activity of the latter in terms of clotting time, since the speed of clotting is a function of the concentration of thrombin. From the equation:

Prothrombin + thromboplastin + calcium = thrombin

it can be postulated that if both calcium and thromboplastin be kept constant, the rate of thrombin formation becomes proportional to the concentration of prothrombin. Incidentally, Eagle[23] has demonstrated that the amount of thrombin formed is independent of calcium and platelets but varies directly with the plasma factor (prothrombin). By employing oxalated plasma and recalcifying with a fixed and optimal quantity of calcium, this factor is made constant. On adding an active preparation of thromboplastin, a maximum acceleration in coagulation time is obtained even with an exceedingly small amount, and, significantly, further addition will not shorten the clotting time, as shown by Table 1. Thus, with the addition of a fixed quantity of calcium and an excess of thromboplastin, prothrombin is the only variable and the clotting time of oxalated plasma under these conditions can be considered a direct measure of the prothrombin concentration of the blood. On this basis the following test was developed.

TABLE 1.—THE PRODUCTION OF A CONSTANT MINIMUM CLOTTING TIME BY THE ADDITION OF THROMBOPLASTIN TO PLASMA.

Thromboplastin* added cc.	0.00†	0.002	0.01	0.02	0.05	0.10	0.20
Clotting time sec.	110	40	22	22	22	22	22

Prothrombin Determination. Nine cubic centimeters of blood, withdrawn rapidly and with special precaution to avoid trauma, are promptly and thoroughly mixed with 1 cc. of M/10 sodium oxalate, and centrifuged at a low speed for 5 minutes. Of this plasma 0.1 cc. is transferred to a dry clean test tube (13 by 100 mm.), and mixed with 0.1 cc. of thromboplastin solution. Then, 0.1 cc. of M/40 calcium chlorid is added, and the tube quickly shaken, and placed in a water bath kept at 37° C. The exact time required for the formation of a solid clot is recorded. With an active preparation of thromboplastin, as will be described, normal human plasma will clot consistently in 22 to 25 seconds.‡

If the assumption is correct that the clotting time is dependent on the prothrombin concentration, any dilution of plasma should produce a delay in the coagulation rate. This actually occurs as

* 10% aqueous emulsion of rabbit brain heated to 60° C.

† Mixed with 0.1 cc. human plasma, and 0.1 cc. M/40 calcium chlorid.

‡ A thromboplastin of this degree of activity was consistently obtained using a series of more than 20 rabbits secured in New York City. Thromboplastin prepared from rabbits now obtained in Milwaukee has an equally consistent but distinctly great activity. It will clot human plasma in 16 to 17 seconds and that of rabbits and dogs in 7 to 9 seconds. This finding does not, however, alter the correctness or significance of the results presented in this paper.

is seen in Table 2. In spite of the excess thromboplastin, the clotting time increases as the plasma is diluted, so that when the prothrombin has been reduced to $\frac{1}{5}$ of normal, the clotting time is increased to 65 seconds. In order to guard against the possibility that the prolonged clotting is due to dilution of some other constituent in the plasma, dilutions were made with both normal saline solution and with plasma that had been treated with aluminum hydroxid. This reagent removes or inactivates prothrombin without apparently causing any other demonstrable change.[24] Thus, a plasma treated with sufficient aluminum hydroxid can be considered as a prothrombin-free plasma. Since the results with either diluent are the same, it seems reasonable to conclude that the decrease in prothrombin concentration alone is responsible for the prolonged clotting time. Interestingly, while undiluted human plasma on recalcification clots in 22 to 25 seconds when excess thromboplastin is present, rabbit's plasma under these conditions will clot in 12 seconds and dog's in 10 seconds. This indicates that the concentration of prothrombin in the blood of these two animals is much higher than in the human. When 1 part of rabbit plasma is mixed with either 8 parts of normal saline or with prothrombin-free plasma (treated with aluminum hydroxid), the resulting mixture will in the presence of added thromboplastin clot in 25 seconds. Since undiluted human plasma will clot in that time, it suggests that rabbit plasma contains about 9 times as much prothrombin as that of man.

TABLE 2.—PROGRESSIVE DILUTION OF PLASMA AS A MEANS OF DEMONSTRATING THE EFFECT DIMINISHING CONCENTRATIONS OF PROTHROMBIN HAS ON CLOTTING TIME.

Normal plasma cc.	Saline solution cc.	Clotting time* seconds.	Clotting time with excess thromboplastin† seconds.	Normal plasma cc.	Prothrombin-free plasma‡ cc.	Clotting time* seconds.	Clotting time with excess thromboplastin† seconds.
0.5	0.0	120	23	0.5	0.0	120	23
0.4	0.1	110	30	0.4	0.1	115	31
0.3	0.2	115	35	0.3	0.2	115	35
0.2	0.3	115	45	0.2	0.3	130	45
0.1	0.4	150	65	0.1	0.4	150	65

* By the unmodified method for determining the clotting time of recalcified plasma.
† By the new prothrombin method.
‡ Plasma treated with aluminum hydroxid.

Determination of the Clotting Time of Recalcified Plasma. By omitting the addition of excess thromboplastin, but otherwise following the directions of the method outlined for the determination of prothrombin, one determines the clotting time of recalcified plasma, which for normal plasma is from 90 to 130 seconds. This method is still commonly called Howell's Prothrombin Time. The term, however, is unfortunate since this method apparently does not determine prothrombin; in fact, the thromboplastin derived principally from the platelets is an even more important factor influencing the clotting time than is the prothrombin. This can

readily be demonstrated, for on centrifuging oxalated plasma at a high speed, its clotting time on recalcification may become 3 times as long as that of the same plasma centrifuged at such a speed that practically no platelets are removed. Nygaard[25] observed that within limits the clotting time runs roughly inversely proportional to the number of platelets remaining in the plasma. Thus, the mechanical removal of the platelets is sufficient to alter profoundly the clotting time, although there is obviously no diminution of prothrombin, but only of thromboplastin. Moreover, by diluting plasma with saline solution or prothrombin-free plasma, no significant change in clotting time occurs until the prothrombin is reduced to nearly $\frac{1}{5}$ of normal, this demonstrating that the method is altogether useless for estimating prothrombin, in contrast to the new prothrombin test which responds promptly even to a relatively small diminution of prothrombin. Nevertheless, the older method is clinically valuable. The prolonged clotting time of recalcified hemophilic plasma which was first observed by Howell[26] has been repeatedly confirmed. The application of the test to cases of jaundice for the detection of a hemorrhagic diathesis was found successful by Bancroft, Kugelmass, and Stanley-Brown,[27] Lewisohn,[28] and Nygaard.[29] Bancroft and Stanley-Brown[27, 30] have further observed that a threatening impending postoperative thrombosis may be indicated by an abnormal shortening of the clotting time.

Preparation and Properties of Thromboplastin. For carrying out the new prothrombin test successfully, it is necessary to prepare an active and stable thromboplastin. Rabbit brain was found to be the most satisfactory source, since it is not only very active, but it can be preserved in the dry state for weeks with little deterioration in activity. The preparation is as follows: the brain of a freshly killed rabbit is freed of the larger superficial bloodvessels, washed, then ground to a paste, and spread in a thin layer on a plate glass, or a flat dish. After thoroughly drying at 37° C., the material is removed from the plate, and preserved in a stoppered container. By mixing 0.2 gm. of this material with 0.3 cc. of 0.85% sodium chlorid, and incubating for 15 minutes, an emulsion is obtained which has practically maximum activity, *i. e.*, it will when added to human plasma cause clotting in 22 to 25 seconds. Any preparation which fails to show this activity is discarded. A fresh emulsion prepared from rabbit brain, thymus, or lung, and heated to 60° C. for 15 minutes to inactivate any prothrombin which may be present, likewise brings about clotting in 22 seconds, thus suggesting that the thromboplastin in these 3 tissues is identical. For the test either the fresh or the dry preparation may be employed. Attempts to purify or isolate the active constituent invariably led to a diminution of activity, and since the product contains no impurity which would interfere with the present problem no further attempts at purification were deemed necessary.

Thromboplastin appears to be, as Howell and Cekada[31] suggested, a cephalin-protein compound. It is not, as is often stated, free cephalin. In the absence of prothrombin, it will not clot fibrinogen. The aqueous emulsion when extracted either with ether or petroleum ether loses no activity, nor is any thromboplastic activity found in the ether extract. The dry preparation, however, is totally inactivated when extracted with these immiscible solvents, and the extract will be weakly active in accelerating clotting.

Thromboplastin undoubtedly is an important factor that must be considered in the problem of the maintenance of the fluidity of intracorporal blood. Circulating blood contains fibrinogen, calcium, prothrombin, and platelets, but no free thromboplastin as long as the platelets remain intact. Even if a small amount of thromboplastin were liberated and a corresponding amount of thrombin formed, clotting would not occur immediately, for it requires even 4 to 5 minutes for blood to clot in a test tube. Clotting is dependent upon the concentration of thrombin, and in circulating blood, any thrombin formed is under normal conditions diluted sufficiently to be ineffective in forming a clot.[32] As a further protection to the individual, any formed thrombin is normally removed at a rate which prevents a dangerous accumulation. It is, therefore, unnecessary to postulate the existence of any antithrombin or antiprothrombin to explain the fluidity of blood. The fact that thrombin must reach a certain concentration before clotting can take place is sufficient protection against intravascular clotting, provided no general or localized circulatory disturbances are present. It seems certain that the disintegration of platelets is necessary for clotting, and that an important factor in this process is contact with roughened surface. The smooth endothelial lining of the vascular system plays an important function in keeping blood fluid. A roughened or calcified intima may produce clumping and lysis of platelets that may give rise to clotting. The laying down of fibrin in an aneurysm sac can readily be explained. The rough surface favors platelet lysis and the local eddies and stagnation of the blood allows sufficient thrombin to accumulate to cause clotting in the aneurysm sac without extension into the normal lumen. In external hemorrhage, clotting occurs because not only does the roughened surface favor platelet lysis, but also because additional thromboplastin is available from the injured tissue. Is it not possible that the rich content of thromboplastin in such tissues as brain and lung is a useful factor in guarding against extensive hemorrhage in organs where even moderate bleeding is serious, and further that the presence of thromboplastin in saliva plays a useful rôle when the wounded animal licks its wound?

Hemophilia. In studying the plasma of 6 hemophilia patients with the new test for prothrombin, normal results as regards quantity of this constituent were obtained in every case. No matter

how much the clotting time was prolonged, hemophilic plasma after the addition of excess thromboplastin clotted normally, *i. e.*, in 22 to 24 seconds (Table 3). Similar results were obtained using whole blood and employing the technique of the Lee White method with the modification that in one tube 0.1 cc. of thromboplastin was added. The results recorded in Table 4 show that even when the clotting time was 10 times longer than normal it became the same as that of ordinary blood when thromboplastin was added.

TABLE 3.—THE EFFECT OF THROMBOPLASTIN ON THE CLOTTING TIME OF HEMOPHILIC PLASMA.

	Clotting time* seconds.	Clotting time with excess thromboplastin seconds.
Normal	110	22
Case I	330	22
Case II	260	23
Case III	405	22
Case IV	210	22
Case V	270	24
Case VI	205	22

* Of recalcified plasma.

From these results it can be concluded that hemophilic blood contains a normal concentration of prothrombin. The question remains, however, whether the defect of hemophilic blood lies in a qualitative peculiarity of the prothrombin, as Addis[6] postulated, which makes it resistant to activation, but which can be overcome by excess thromboplastin; or whether there is a deficiency in thromboplastin. As normal plasma can be made to clot normally with hemophilic platelets, a possible prothrombin defect must be kept under consideration. An abnormal stability of the platelets against lysis or a diminished prothrombin content could cause a thrombo-

TABLE 4.—THE CLOTTING TIME OF WHOLE BLOOD IN HEMOPHILIA. THE EFFECT OF THROMBOPLASTIN.

	Lee White method.	
Subject.	Unmodified seconds.	With added thromboplastin* seconds.
Normal	210	30
Hemophilia Case I	1260	45
Hemophilia Case II	2260	24

* 0.1 cc. thromboplastin emulsion added to 1 cc. of blood.

plastin deficiency. The work of Sahli,[7] Wöhlisch,[33] Minot and Lee,[34] and others support the hypothesis that the platelets of a hemophilic patient are less active than those of a healthy individual. Fonio[35] once held the view that the hemophilic platelets contain less thrombocyme (thromboplastin), but recently[36] has concluded that the stability of the platelets is responsible for hemophilia. Howell and Cekada[31] also attribute the delayed clotting to a slow disintegration of platelets. Interestingly, the tissues other than platelets

of a hemophilia patient appear unquestionably normal in regard to their thromboplastin content. Minot and Lee,[34] and Lowenberg and Rubenstone[37] found that the organs of a hemophilic patient had the same content of thromboplastin as those of a normal individual. The saliva of one of our hemophilia cases had a very active thromboplastic action; 0.1 cc. of his saliva clotted recalcified human plasma in 22 seconds, whereas the saliva of normal individuals often only produced clotting in 50 seconds.

The treatment of hemophilia is still very unsatisfactory. While it is clear that an excess of thromboplastin makes hemophilic blood clot normally, no method is known for supplying this substance except locally. There is no way to increase the thromboplastin content of platelets or to alter their stability. Blood transfusion remains the most reliable therapeutic measure for combating hemorrhage, and Minot and Lee[34] found that after a transfusion, the clotting time of a hemophilic became normal for a few days. Nevertheless, it is often found that hemorrhage persists after transfusion. This can probably be explained as follows. The amount of available thromboplastin from platelet lysis even in normal blood is relatively small, and therefore it is difficult to supply sufficient blood to correct the defective hemophilic blood. The newer methods of treatment, such as sensitization to a foreign protein, administration of the follicular hormone, theelin, and injection of snake venom still require further study before their value can be estimated. Active thromboplastin can be effectively used in any hemorrhage which can be approached locally. Parenterally it is unsatisfactory and may even be dangerous. It is doubtful whether intramuscular injection has any demonstrable beneficial effect, and intravenous administration is distinctly hazardous. If the preparation is active, it may cause extensive intravascular clotting, or cause a sudden disappearance of the fibrinogen such as we produced in the dog.

Jaundice. In studying the plasma from various types of jaundiced patients by the new method for determining prothrombin, it was found that this component was often greatly diminished, as illustrated in Table 5. Instead of obtaining a normal clotting time of 22 to 25 seconds, a delay, which in 1 case was as long as 90 seconds, was obtained. Significantly, the clotting time of recalcified plasma without the addition of extra thromboplastin was only slightly prolonged, thus giving no intimation of the extent that prothrombin had been diminished. As already pointed out when discussing the results of Table 2, the prothrombin factor has a wide margin of safety, and the component can be greatly diluted or diminished before a marked delay in clotting time occurs. Nevertheless, it has been shown by Lewisohn,[28] Nygaard[29], and us, that the plasmas of patients that develop so-called cholemic hemorrhages show a prolonged clotting time on recalcification. The delay is not due to insufficient thromboplastin, for it is clear from the present

studies that excess thromboplastin does not restore the normal clotting rate as it does in hemophilic plasma. These findings therefore suggest that the hemorrhagic tendency in jaundice is brought about by a diminution of prothrombin. Further work is required, however, before this conclusion can be definitely established; nevertheless, it can be used as a working hypothesis both for theoretical and clinical studies. Thus, the beneficial results from blood transfusions, which are well recognized clinically, can be readily explained. Because of the wide margin of safety in the prothrombin concentration, which has already been emphasized, even a partial restoration of the prothrombin will bring about a sufficient shortening of the clotting time to bring it within normal range.

TABLE 5.—THE CLOTTING TIME OF PLASMA FROM JAUNDICED PATIENTS. THE EFFECTS OF ADDED THROMBOPLASTIN.

Diagnosis.	Clotting time* seconds.	Clotting time with added thromboplastin seconds.
Normal	110	23
Carcinoma of biliary tract	210	85
Stenosis of common duct	150	37
Chronic hepatitis and stenosis of common duct	140	90
Carcinoma of head of pancreas	150	50
Liver abscess	120	35

* Of recalcified plasma.

Summary. On the basis that the rate of clotting is proportional to the concentration of thrombin, and that this agent is formed by the interaction of prothrombin, thromboplastin, and calcium, a new method for estimating prothrombin has been developed. By employing oxalated plasma, recalcifying with an optimal amount of calcium, and adding an excess of thromboplastin, prothrombin become the only variable in the reaction and the amount of thrombin formed depends on the concentration of prothrombin. The clotting time, therefore, becomes a direct measure of the prothrombin.

By means of this new test it has been found that the prothrombin concentration in the blood of normal individuals is remarkably constant, but much lower than in dog's and rabbit's blood.

In hemophilia the prothrombin was found normal in quantity, *i. e.*, the clotting time of hemophilia plasma clotted in the same time as normal plasma, when excess thromboplastin was added. In the plasma of various types of jaundice a delayed clotting rate in the presence of excess thromboplastin was obtained, suggesting that the hemorrhagic tendency in jaundice is caused by a diminution of prothrombin.

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(Titles have been omitted for sake of brevity.)

GAUCHER'S DISEASE OF LATE ONSET WITH KIDNEY INVOLVEMENT AND HUGE SPLEEN.*

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Case reports and discussion of Gaucher's disease have occupied a fairly prominent position in the literature during recent years. The total number of cases reported is not large, however, and it seems worth while to record this case, particularly since it showed several unusual features.

* Presented before the Richmond Academy of Medicine, January 8, 1935.

Case Report. *History.* A white farmer, aged 47, was admitted to the Sheltering Arms Hospital on May 18, 1934, complaining of a large mass in the abdomen and aching in both legs. There was no history of any familial diseases. His mother died of pneumonia and father of kidney disease. All of his 4 brothers and sisters are living and well. His wife died of puerperal sepsis, leaving 5 healthy children. The patient was in excellent health prior to his present illness. He had the usual diseases of childhood, but no other definite illnesses that he could remember. Jaundice and any symptoms of malaria or venereal diseases were specifically denied. Since the patient was born in the southwestern part of Virginia and had lived there all his life, the possibility of having contracted any tropical diseases seemed remote. He is not known to have had any Jewish ancestry.

The present illness started about 12 years ago when the patient noticed enlargement of the abdomen. He was then examined by Dr. E. M. Corns, of Kingsport, Tennessee, who found an enlarged spleen. The enlargement of the abdomen at that time had come on gradually during the preceding 4 months. This was accompanied by loss of several pounds in weight, weakness, and the development of a copper color in the skin. The loss in weight and the weakness were attributed to repeated hemorrhages from the intestinal tract which had occurred over a period of 2 months. From 1 to 5 times a day he would pass from a pint to a quart of bloody, "flesh-like" stools. After this illness of 2 months he rapidly gained in strength and weight. There was no further bleeding from the gastro-intestinal tract, and no hemoptysis or hematuria. Repeated hemorrhages beneath the skin and mucous membranes started 7 years after the enlargement of the abdomen was first noticed and during the last 5 years of his illness progressively increased in frequency and severity, especially in cold weather. Mild epistaxis occurred frequently throughout the 12 years of his present illness. The aching in both legs began about 5 years before admission and was accompanied by swelling and discoloration, particularly in the right lower extremity, and most markedly about the right thigh and knee. These symptoms would appear with cold weather, usually in the month of December, and would clear up as soon as the weather became warm, so that the patient was able to return to his usual duties on the farm. Three years before admission he complained of severe pain in his right knee and was sent to a hospital to have his spleen removed for Banti's disease. His physician stated that there was no swelling or other signs of injury or abnormality in the knee, but the pain was so severe that the patient had to be given morphin hypodermically for relief. He left against advice soon after admission and before any examinations had been made. The pain in the knee lasted for about 3 weeks and did not return with the same severity. He worked until December, 1933, but from that time to his admission he became steadily weaker, and the discomfort, swelling, etc., in both lower extremities became progressively worse. There was only slight variation in the enlargement of the abdomen during the last 12 years, except that a few months before admission it markedly increased. No mental changes of any consequence were noted until a few months before admission when the patient became sluggish and extremely depressed over his condition.

Treatment previous to admission to the hospital was merely symptomatic and palliative.

Physical Examination. The patient was rather poorly nourished and decidedly emaciated. He seemed to be quite ill. The skin was pale and showed slight jaundice, multiple petechiæ and several large subcutaneous hemorrhages. The typical yellow wedge-shaped pingueculæ were present in both scleræ. The pupils reacted sluggishly. The gums were swollen and hyperemic and bled easily. The lungs were essentially normal. Except for a soft systolic murmur over the tricuspid area, examination of the heart

was entirely negative. The blood pressure was 110 systolic and 85 diastolic. There was a mass in the abdomen which extended from above the costal border down into the pelvis, occupying the entire left side of the abdomen and extending about 2 to 3 cm. to the right of the midline. A definite notch could be palpated on the medial side of this tumor. The liver was palpable 2 to 3 cm. below the costal border. There was no abdominal tenderness and no demonstrable ascites. Both legs showed a brownish pigmentation. The right leg and thigh were edematous, and the right knee showed a firm diffuse swelling which was quite tender, probably caused by a hemorrhage into the joint capsule.

Laboratory Examinations. On admission, the hemoglobin was 42%; red blood count, 2,750,000; white blood count, 2300; neutrophils, 83%; lymphocytes, 12%; large mononuclears, 2%; eosinophils, 2%; basophils, 1%. Urinalyses were essentially negative. Subsequent examinations of the blood showed a progressive anemia and leukopenia. The blood Wassermann reaction was negative.

Treatment and Course. The patient's condition grew steadily worse from the time of admission. Temperature ranged between 96° and 99° F. Liver extract and iron had no effect on his anemia. Calcium gluconate given intravenously seemed to lessen the tendency to bleeding and relieved temporarily the pain in the knee. Later large doses of morphin were necessary to control the pain. During the last few days before death, he was irrational and confused. On June 11 (24 days after admission), he developed signs of pulmonary edema and died in a few hours.

Autopsy (Dr. Kinloch Nelson, 7 hours after death, the body having previously been embalmed). The appearance was that of a very emaciated, middle-aged, white man. Palpation of the abdomen revealed a large smooth mass extending from under the costal margin down to the left iliac crest and about 3 cm. to the right of the mid-line.

The pleural surfaces were smooth and glistening; lungs unusually pale except for hypostatic congestion of both bases posteriorly. On section much edematous fluid escaped. The pericardium was smooth and glistening with increased subepicardial fat and moderate coronary sclerosis. The myocardium and valves were grossly normal except the cusps of the aortic valve which were thickened and hardened, resulting in the amalgamation of two cusps in a hard, partially calcified mass. Aorta appeared normal.

The peritoneal surface was smooth and glistening, and contained about 500 cc. of clear thin yellowish fluid. The spleen was enormously enlarged, weighing 5890 gm. It measured 38 by 20 by 13 cm. and completely filled the entire left side of the abdominal cavity. Its surface was smooth, deep blue in color, with white spots irregularly scattered over it, and near the hilum a large white or pale yellow, soft area, about the size of an orange. On section the splenic substance appeared dark red or bluish, and firm. The pale area near the hilum on section was entirely composed of a whitish-yellow and apparently fatty substance. The splenic vessels were much enlarged and tortuous. The liver was large, dark brown, irregular and firm, and had the appearance of cirrhosis. The stomach, duodenum, small and large intestines were grossly normal. The appendix was represented by a short stump of atrophic sclerotic tissue. The pancreas was small but grossly normal. Both kidneys were somewhat enlarged, capsules stripped readily leaving a finely granular surface and were grossly normal on section. Ureters, bladder and prostate were normal.

Microscopic Examination (Dr. F. L. Apperly). *Spleen* shows the typical picture of Gaucher's disease, but in a most advanced stage. Practically the entire field is occupied by Gaucher cells, with large round pale cytoplasm and small darkly staining round or oval nucleus eccentrically placed. The cytoplasm appears to contain a fine network of fibrils. These

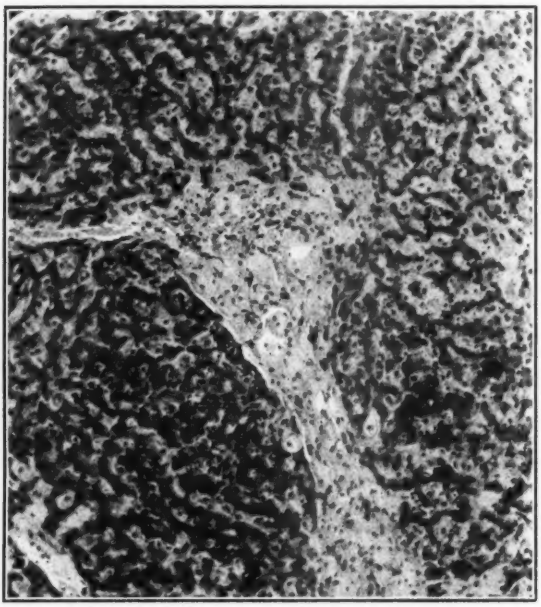

FIG. 1.—Photomicrograph of liver (× 130) with masses of Gaucher cells lying between liver lobules and in places apparently invading the sinusoids. Liver parenchyma somewhat degenerated.

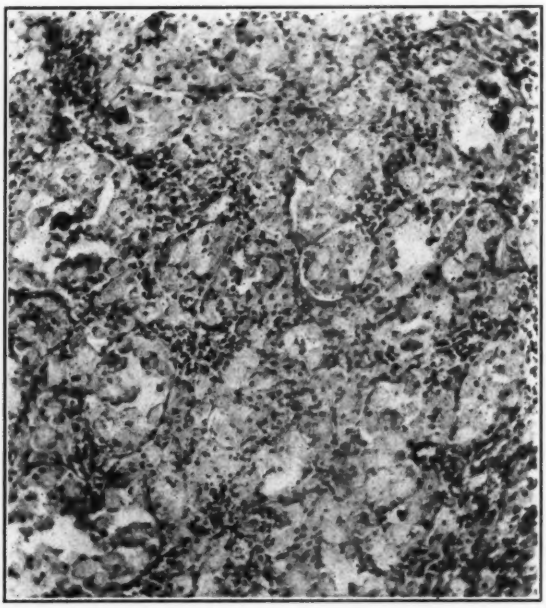

FIG. 2.—Photomicrograph of spleen (× 120) with large pale Gaucher cells crowded into alveoli. Two areas show cells containing a considerable amount of hemosiderin pigment. A few cells of spleen pulp lie between the Gaucher masses.

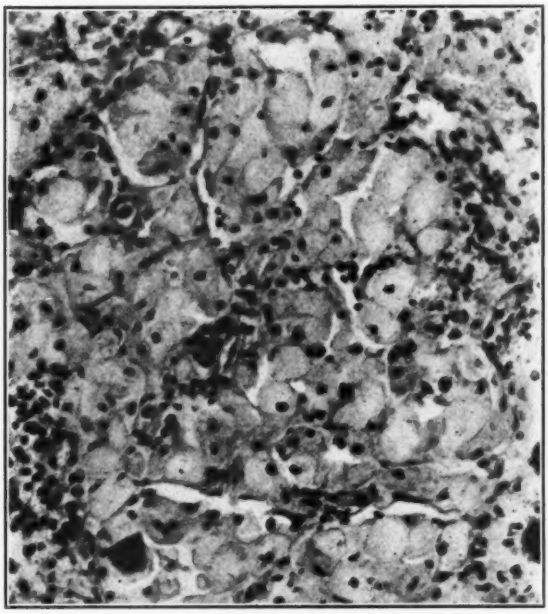

FIG. 3.—Photomicrograph of spleen (× 260), same field as Fig. 2, with characteristic Gaucher cells, large and round, with very pale cytoplasm and small, round or oval, eccentric nucleus. Cells often crowded into alveoli.

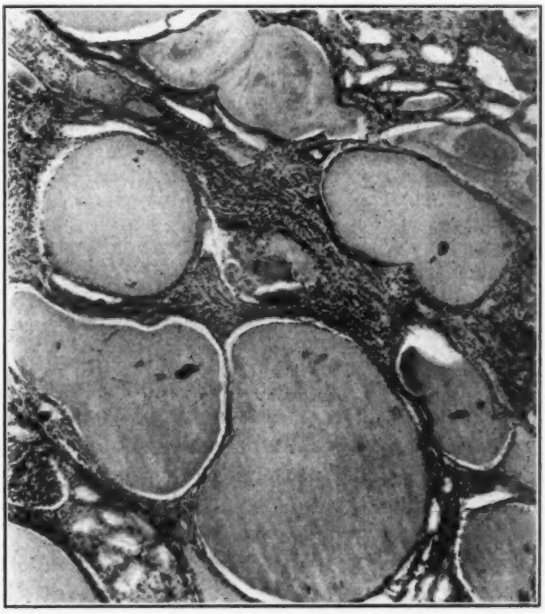

FIG. 4.—Photomicrograph of kidney (× 75) section from one area showing (in center) a group of large pale cells (Gaucher cells?) crowded into an alveolus. Note also cystic dilatation of many kidney tubules containing a coagulum.

cells seem crowded into distended spaces, in some of which are broken-down cells and dark pigment, extracellular and intracellular. The normal splenic substance is almost crowded out of existence (Figs. 2 and 3). The white necrosed area consists of a Gaucher cell complex, now quite necrosed, in which the general structure typical of a Gaucher's spleen is readily made out in ghostly outline. Stain for iron by potassium ferrocyanid shows that in the spleen Gaucher cells stain pale blue, but in the liver there are large areas in which these cells are completely unaffected, while in others only a faint blue color is observed. Contrasting with Pick's descriptions, there is no iron stain in the splenic trabeculæ or endothelial cells of venous sinuses. With scarlet red, which shows bright red in the presence of true fats, and a paler different tint in the case of cholesterin—esters and cholesterin—fatty acid mixtures, the Gaucher cells stain a pale orange, which we may take as indicating the presence of cholesterin bodies in small amount. This is very noticeably more marked in the splenic necrotic area, especially under the capsule, than in other parts of the spleen (Table 1).

TABLE 1.

Analyst.	Cholesterol per cent dry weight.			Ether insoluble-alcohol soluble material, per cent dry weight.		
	Normal spleen.	Gaucher cells.	Degenerated areas.	Normal spleen.	Gaucher cells.	Degenerated areas.
The Authors	1.7	1.8	3.9	9.8	26.0	14.7
Bloom and Kern	2.4	2.6	...	17.6	22.4	...
Lieb	...	...	...	13.1*	35.0*	...

* Calculated on dry weight of ether extracted material.

Liver substance is shot through with areas of Gaucher cells lying along the interlobular borders but with some invasion along the sinusoids of the lobules, and apparently causing obstruction and parenchymal atrophy (Fig. 1).

Kidney sections show glomerular hyperemia, and tubular degeneration mainly. In one section, however, there are large cystic spaces, resembling hugely dilated tubules almost filling the low-power field, and lined with a low flattened epithelium, embracing an eosinophil coagulum. The remainder of the section shows the changes found in ischemic nephritis. In one section, however, a small space is seen filled with cells indistinguishable from Gaucher cells. Gaucher cells in the kidney have heretofore never been reported (Figs. 4 and 5).

Pancreas shows a normal parenchyma, but irregularly sclerosed arteries, with patchy calcification.

Lung section show no significant changes.

Bone marrow from the sternum shows no Gaucher cells, but a normal marrow.

Chemical Analysis. Dr. J. C. Forbes, Associate Professor of Chemistry, has kindly made a chemical analysis of the spleen. Samples were taken from formalin-hardened material of (*a*) normal spleen (*b*) a typical Gaucher area, and (*c*) an area in the Gaucher spleen which microscopically was seen to be composed of necrosed Gaucher cells.

The material was finely cut up, dried at room temperature, and pulverized. It was then extracted in a Soxhlet apparatus, first with ether, then with alcohol. Cholesterol was determined colorimetrically in the residue after ether extraction. The alcohol extract was

evaporated to dryness and the residue weighed. This material has not been further purified. It is, however, undoubtedly high in cerebrosids since it readily reduces Benedict's solution after hydrolysis with hydrochloric acid.

FIG. 5.—Photomicrograph of kidney (× 260), same field as Fig. 4, showing details of group of Gaucher cells in kidney.

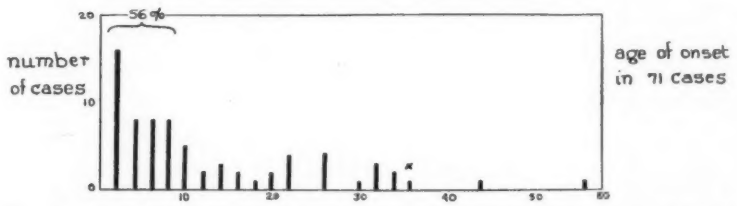

FIG. 6.—Graph constructed from 71 cases of Gaucher's disease, collected from the literature, showing the number of cases in each 2-year age period at which the disease was first noticed.

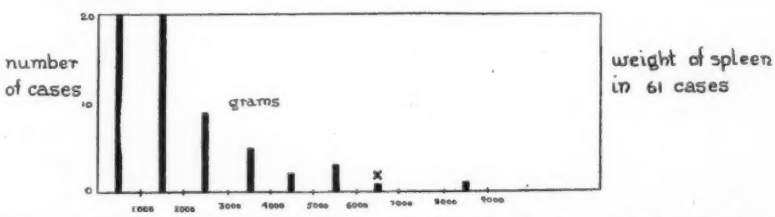

FIG. 7.—Graph constructed from 61 cases of Gaucher's disease in the literature showing the weight of the spleen where it is recorded.

In Table 1 our results are compared with those of Bloom and Kern,[6] and of Lieb.[7]

A. Cholesterol. Our figures, and those of Bloom and Kern, show that there is no notable increase of cholesterol in the live lesions of Gaucher's disease, which is in keeping with the results found in our stained sections. In the necrotic area, however, the cholesterol content is doubled, possibly due to disintegration and partial absorption of cellular debris, the cholesterol remaining behind.

B. The ether—insoluble—alcohol—soluble fraction, which includes the cerebrosid, kerasin, is increased to about 2 to 2½ times the normal, though in the degenerated necrotic areas it is increased to only a small extent above normal. It is possible that in these necrosed areas the lipoids are hydrolyzed into their constituents, some of which are readily absorbed.

Remarks. This case is remarkable for the following reasons: 1. The age of the patient. We have constructed a graph (Fig. 6) from 71 cases collected from the literature, showing the number of cases in each 2-year age period, at which the disease was first noticed. The graph shows that 56% of these cases appeared at or before the age of 8 years. Our patient was 35 when the disease was first noticed. Among these cases only 2 (aged 44 and 56) were older than our patient.

2. The size of the spleen. We have constructed another graph (Fig. 7) showing the weight of the spleen in 61 cases in the literature where this is recorded. Only twice has a spleen of greater mass than that of our patient been recorded. These spleens weighed 8100 gm. and 6250 gm. as against that of our case, with a weight of 5890 gm.

3. The appearance in the kidney of an area apparently composed of Gaucher cells. These cells, besides appearing in spleen, liver, bone marrow and lymphoid tissue, have occasionally been reported in the thymus, lungs and even cerebral cortex, but in no case have these cells been reported in the kidney.

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HYPERPARATHYROIDISM WITH RENAL INSUFFICIENCY.

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Since Mandl's[1] classical description of his case of hyperparathyroidism, the subject has appeared more and more frequently in the literature. To date, more than 100 carefully described cases have been reported. Of these, many have been successfully operated upon, and startling clinical improvement has been noted. The syndrome is so protean in its manifestations, and tends to simulate other medical conditions so closely, that it is frequently overlooked. This oversight is regrettable because therapy for hyperparathyroidism is so successful.

Albright[2] divided his group of cases into six types: 1, Classical hyperparathyroidism (von Recklinghausen's disease); 2, osteoporotic form of hyperparathyroidism; 3, hyperparathyroidism with nephrolithiasis; 4, acute parathyroid poisoning; 5, hyperparathyroidism simulating Paget's disease; 6, hyperparathyroidism with renal insufficiency (only 1 case of this type is presented in his series).

We present herewith a case of hyperparathyroidism with marked renal insufficiency. Removal of an adenoma of a parathyroid gland was followed by improvement.

Case Report. D. C., white, female, American, aged 44, a housewife, was admitted to this hospital July 3, 1934. For 1 month she had had numerous and varied complaints, chiefly pain in the legs radiating down from the knees, inability to stand, tenderness over the bones, pain on moving the joints with indefinite muscle pains, and a tumor of the left lower jaw (which was diagnosed as an epulis on biopsy). She complained also of frequency and nocturia, micturating almost every hour, with polyuria and a reversal of the day and night ratio, but at no time did she have any edema. There was marked anorexia, and a loss of 60 pounds in the past year, making her so weak that she lacked the strength to walk around. She was chronically constipated and frequently vomited food soon after meals. She also had dyspnea on slight exertion, precordial pain relieved by resting, and palpitation. Her mental state was one of constant anxiety, irritability and emotional instability. Her vision had been good, although her eyes showed chronic conjunctival congestion. She was absolutely definite in stating that her hearing was markedly impaired since all these peculiar things were happening to her.

Examination of the patient at the time of admission showed the temperature to be 100°, respiration 22, blood pressure 110/74. Physically, the patient showed only marked evidence of emaciation and loss of weight, and an epulis in the left mandible which was large, hard and smooth, reaching above the level of the biting edge of the teeth. There were arterio-

sclerotic changes in the eyegrounds, and both eardrums show calcification, more on the right side, where almost complete deafness existed. The muscles were flabby, with a marked decrease in muscle tone.

Laboratory Studies. The kidney function test showed an increased night specimen with specific gravity at 1.009 and below. The dye excretion was greatly decreased, being less than 5% after 2 hours. Roentgen rays of the chest and of the gastro-intestinal tract were negative. The blood sugar was 108.1 mgm.; urea nitrogen, 31.4 mgm.; creatinin, 2.5 mgm.; uric acid 4.3 mgm. The basal metabolic rate was +8. The blood Wassermann reaction was negative. The leukocyte count was 10,000 with 80% neutrophils, 18% lymphocytes, and 2% transitional cells; red blood count 4,540,000; hemoglobin 75% (Dare). The urine contained a very faint trace of albumin and 20 to 35 pus cells per high-power field with numerous bacteria. The electrocardiogram was normal. The weight was 114 pounds.

On high vitamin diet and supportive and symptomatic treatment, the patient improved somewhat and was discharged August 1, with the following diagnoses which, at the time, were felt to be unsatisfactory: chronic nephritis, epulis, menopause.

She was readmitted on September 10, with the story of having been bedridden since her discharge, and of having had an exacerbation of all the symptoms enumerated previously, which had subsided while in the hospital. On examination, the patient showed even more emaciation, marked cachexia, the epulis was greatly increased in size, and there was a generalized hemorrhagic eruption.

Laboratory Studies. The blood Wassermann reaction was negative; the leukocyte count was 9800 with 72% neutrophils, 26% lymphocytes, and 2% transitional cells; red blood count was 2,950,000; hemoglobin 60% (Dare). The urine showed 1+ albumin and pus cells too numerous to count, with many bacteria. The blood pressure was 110/74. The carbon dioxid combining power was 40%. The blood sugar was 95.2 mgm., urea nitrogen 58.8 mgm., uric acid 4.7 mgm., and creatinin 2.8 mgm. The weight was 90½ pounds. The kidney function test was essentially the same as on the first admission. The sedimentation time was 20 minutes, the bleeding time was 2 minutes, the coagulation time 5 minutes. The platelet count was 320,000 per c.mm. The Bence-Jones protein reaction was repeatedly negative.

No other physical or laboratory findings were obtained to aid in the diagnosis. At this time the general opinion was in favor of a systemic disease only secondarily affecting the kidneys, and the following possibilities were considered: avitaminosis, malignancy, kidney anomaly, calcium deficiency, malnutrition and starvation with mild acidosis. A blood calcium determination taken September 15th to rule out the diagnosis of avitaminosis and calcium deficiency disclosed a serum calcium of 19.5 mgm. per 100 cc. and a phosphorus of 6.8 mgm. This was confirmed on September 19th, when a serum calcium value of 19.6 mgm. was obtained. Thereupon, the diagnosis of hyperparathyroidism was made. Inclusive Roentgen ray pictures revealed no abnormalities in the long bones except somewhat increased trabeculation, and a small cyst in the third metacarpal bone of the left hand (Fig. 3). The skull plates showed osteoporosis and a ground-glass appearance with an accentuation of the inner table (Fig. 1). The ribs also showed definite osteoporotic changes. These findings bear out the statement of Camp[3] that the predominant early changes in hyperparathyroidism occur in the flat bones. Roentgen ray of the jaw in the region of the epulis showed it to be an osteoclastic process (Fig. 2A), and the relationship between the epulis and the general condition was recognized, as was demonstrated by Albright.[2]

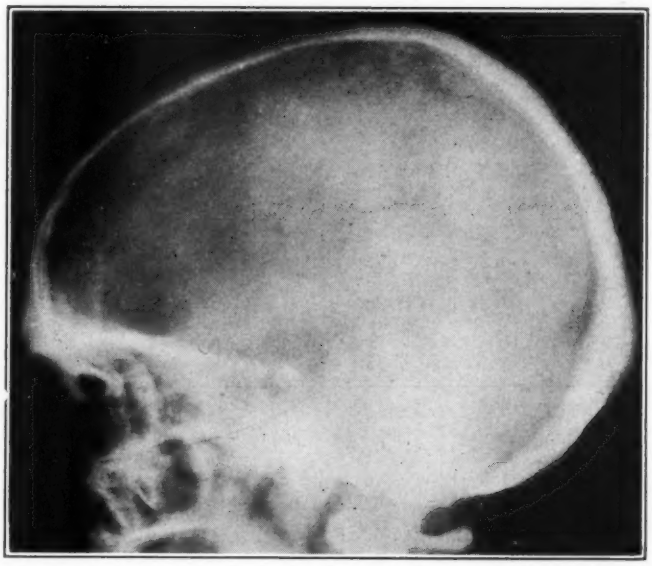

FIG. 1.—The bones of the calvarium show the characteristic changes of hyperparathyroidism, which are mild in this case. There is thickening of the skull in the frontal, parietal and occipital regions, with indistinctness of the inner and outer tables; and definite and marked osteoporosis of the skull, with the classical, granular, ground-glass appearance.

FIG. 2A.—Roentgen ray of the mandible (obliquely from below), the left ramus of which contained the epulis, shows a bone defect in the alveolar region with a sharply outlined contour and no periosteal reaction around it. The surrounding bone shows marked osteoporosis. This was taken pre-operatively.

FIG. 2B.—Four weeks after operation, fibroösteosis is marked, and the repair process is definitely shown in the left ramus of the mandible by new bone formation.

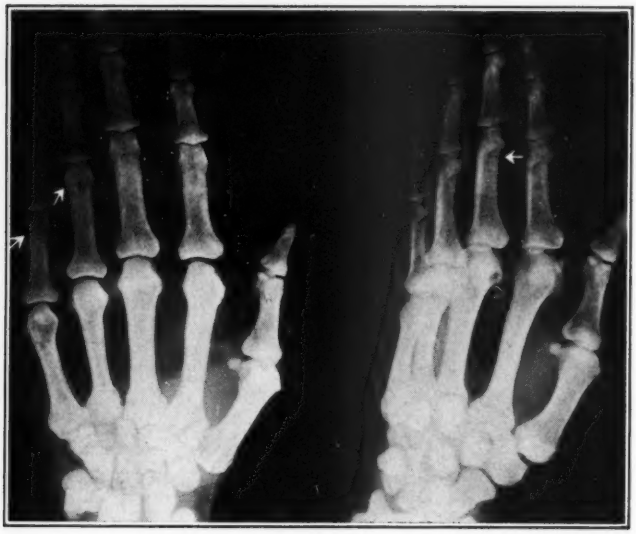

FIG. 3.—Left hand. All the phalanges and the metacarpals show marked osteoporosis. The head of the third metacarpal shows a small bone cyst.

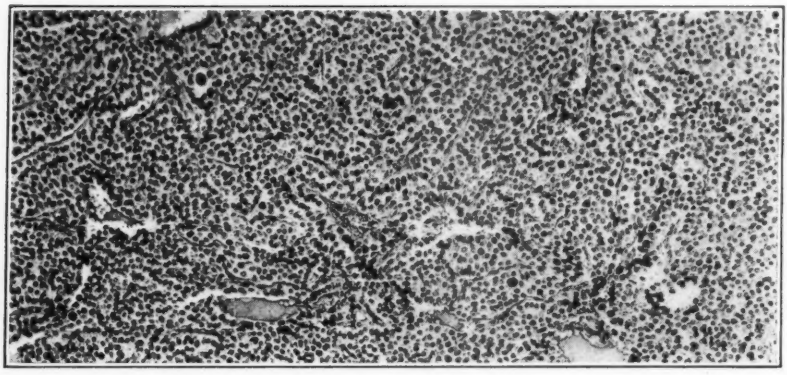

FIG. 5.—Note the hyperplasia of the parathyroid cells with predominance of the oxyphilic cells. Also note the tendency to glandular arrangement of the parathyroid cells at numerous points in the parenchyma. The spaces formed by the latter contain a colloid-like secretion which stains homogeneous pink with hematoxylin and eosin. (× 120.)

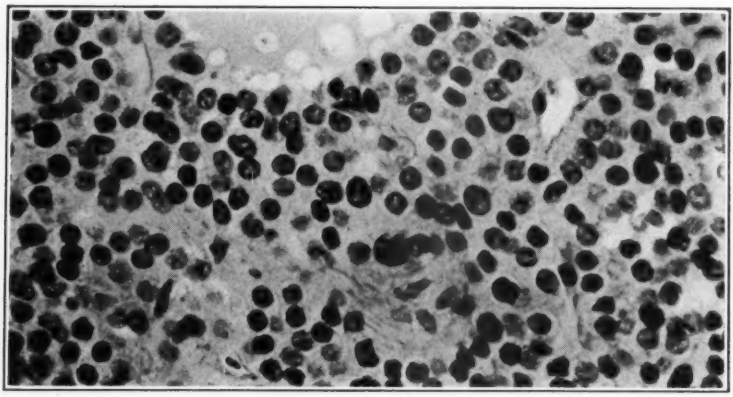

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FIG. 6.—This is a higher magnification of the parathyroid tumor. Note the predominance of the oxyphilic cells and the typical glandular arrangement described above in Fig. 5. (× 400.)

TABLE 1.—BLOOD NON-PROTEIN NITROGEN DETERMINATIONS.

Date.	Urea nitrogen mgm. per 100 cc.	Uric acid mgm. per 100 cc.	Creatinin mgm. per 100 cc.	Blood pressure.	
				Systolic.	Diastolic.
1934					
July 3	31.4	...	2.4	130	94
July 23	26.5	4.3	2.5	114	80
July 30	37.5	...	2.7	112	78
Sept. 12	58.8	4.7	2.7	130	90
Sept. 17	51.7	4.0	2.8	118	72
Sept. 24	49.0	...	3.2	130	90
Nov. 2		Operation			
Nov. 7	75.0	...	4.4	136	90
Nov. 10	79.8	...	4.1	134	90
Nov. 12	60.0	...	2.9	136	88
Nov. 13	66.4	...	2.7	134	84
Nov. 19	43.2	...	2.9	132	90
Nov. 24	62.1	...	2.8	120	80
Nov. 27	66.6	...	3.1	100	70
Dec. 4	57.6	...	3.4	118	90
Dec. 7	60.0	...	3.1	110	80
Dec. 13	68.1	4.2	3.3	130	90
Dec. 15	66.6	...	3.2	104	80
Dec. 27	105.0	4.7	3.8	100	80
Dec. 31	109.0	4.5	3.7	110	84
1935					
Jan. 1	120.5	4.9	3.8	80	60
Jan. 15	107.0	...	2.9	98	64
Jan. 21	89.5	4.7	2.4	90	50
Jan. 23	94.5	...	3.0	100	50
Feb. 5	50.0	4.1	2.6	100	50
Feb. 11	81.5	4.0	2.7	106	70

TABLE 2.—CALCIUM AND PHOSPHORUS DETERMINATIONS.

Date.	Calcium mgm. per 100 cc.	Phosphorus mgm. per 100 cc.	Serum Phosphatase Bodansky units.	24-hr. calcium intake gm.	24-hr. calcium urinary output mgm.
1934					
Sept. 15	19.5	6.8			
Sept. 19	19.6	6.5			
Sept. 22	17.6	6.5			
Oct. 15	16.2	6.5	6		
Oct. 16	....	...	...	4.06	228
Oct. 17	22.0	6.7	...	4.06	372
Oct. 18	....	...	...	4.43	240
Oct. 27	22.0	6.8			
Nov. 2		Operation			
Nov. 7	11.6	6.7			
Nov. 8	11.0	6.6			
Nov. 9	11.4	5.5			
Nov. 10	12.8	5.7			
Nov. 13	11.0	6.8	...	5.3	146
Nov. 14	10.4	5.4	...	5.3	98
Nov. 21	11.2	5.7	...	5.3	178
Nov. 27	10.6	5.3			
Dec. 8	10.5	9.8			
Dec. 15	14.6	8.3			
Dec. 20	9.3	7.1	4.8		
Dec. 22	11.4	8.1			
1935					
Jan. 15	11.4	7.8			
Jan. 16	12.8	8.0			
Jan. 25	12.4	7.0			
Jan. 31	11.7	7.0			
Feb. 7	14.0	7.3			

Swallowing of barium under fluoroscopy showed no filling defect of the esophagus, indicating no impingement of any tumor on the esophagus. The flat plate of the abdomen revealed no calcification, stone, or other kidney abnormality. No finely granular casts, as mentioned by Albright,[4] were ever found.

At this time the urea nitrogen was 58.8, and the serum calcium rose to 22 mgm. on two occasions (Tables 1 and 2). A calcium balance was done. On a high calcium intake, around 4 gm. per 24 hours, the calcium output was essentially normal, varying between 228 and 372 mgm. per 24 hours. The serum phosphatase was 6 Bodansky units, normal being 2 to 4.[8]

The patient was built up by supportive therapy and transfusion, and prepared for operation, which was performed by Dr. C. L. Davidson of the Surgical Service on November 2, 1934, who reports that an adenoma of the left lower parathyroid was found, about $\frac{7}{8}$ inch in length and $\frac{1}{2}$ inch in width, with cystic degeneration. The tumor was dissected free, its blood supply was ligated, and it was excised. The right portion of the thyroid gland was explored and two parathyroids were observed. They appeared to be normal in size and consistency.

FIG. 4.—The parathyroid tumor cut in half. The darker colored upper two-thirds represents the cystlike structure, while the lighter colored lower third represents the hyperplastic parathyroid tissue.

Pathologic Report. (Dr. S. H. Polayes.) (Fig. 4.) The specimen consists of an ovoid cystic mass measuring 3 cm. in its greatest diameter. One-third of the mass is firm in consistency, and the other two-thirds of the specimen consists of a pink mass, which is cystic. Section shows the solid pole to be made up of a finely porous yellow-gray structure which tapers off into fine trabeculæ, the latter traversing the cystic area to the capsule. This produces a multilocular type of cystlike structure, the wall of which is very thin, and within which is contained a brown gelatinoid fluid substance.

Microscopically (Figs. 5 and 6). The tissue consists of parathyroid, the cells of which are arranged in cords with a very fine but rich capillary network. The individual cells answer the description of parathyroid gland, both oxyphil and basophil cells being demonstrable. In areas, there is a tendency to acinar formation with an excessive colloid production. The largest accumulation of colloid is found in the cystic area mentioned in the

macroscopic description. Here the lining of the colloid collection is a thin, fibrous structure, which forms the wall of the cystic pole described above.

Diagnosis. Adenoma of parathyroid.

The microscopic slides were seen by Dr. C. F. Geschickter of the Johns Hopkins Hospital, who concurred in the diagnosis.

Following operation the patient had an uneventful convalescence, and within a few days there was a decided drop in serum calcium to 11.6. The serum calcium has remained at this level fairly constantly. The serum phosphatase was 4.8 Bodansky units. The patient has increased in weight from 83 to 98½ pounds. The deafness, which was total in the right ear and 80% in the left, has completely disappeared. Concomitant with this disappearance, the marked calcific deposits in the ear-drums have also disappeared. The epulis, which previously was large enough to reach the tooth line, has now completely disappeared, and Roentgen rays reveal an increase in osteoid tissue in the mandible, which previous Roentgen rays showed to have a punched-out appearance (Fig. 2B). Her general appearance has changed from one of anxiety and chronic illness to one of general well-being and alertness. The muscle tone has increased to normal.

Despite the marked improvement noted above, there has been no similar improvement in the kidney function. Tests have repeatedly given the same results as were obtained pre-operatively, that is, specific gravity at 1.009 and below, increased night specimen, and dye excretion between 5 and 10% after 2 hours. In addition, there has been noted an ever increasing azotemia (Tables 1 and 2). The last estimation, February 11, revealed a blood urea nitrogen of 81.5, uric acid of 4, and creatinin of 2.7.

Calcium balance determinations were made 3 weeks postoperatively. On an intake of 5.3 gm. of calcium per 24 hours, the calcium output varied between 98 and 178 mgm. per 24 hours.

This case represents one of the less common clinical types of the hyperparathyroid syndrome, which has come to be recognized as a definite clinical entity. Failure to recognize this condition results in hopeless confusion because of its close similarity to chronic nephritis, malignancy, avitaminosis, starvation and malnutrition, congenital kidney anomaly, and the various forms of generalized bony tenderness seen in scurvy in adults and bone malignancies.[7] The outstanding features of this syndrome are: 1, Extreme wasting, despite a balanced diet; 2, azotemia without hypertension; 3, epulis, which may or may not be present; 4, high serum calcium; 5, evidence of osteoporosis, most marked in the flat bones; 6, hypotonia.

We were particularly fortunate, in this case, in finding the hyperplastic tissue in the form of one adenoma which was easily shelled out and removed. Other authors report cases of slight adenopathy in all the parathyroid glands, and even cases of hyperplasia without enlargement of all the parathyroid tissue. The latter cannot be improved by operation.[4]

In our case, there is excessive and marked parathyroid tissue hyperplasia, yet the patient has had a relatively long clinical course which has not ended fatally. The following explanation is offered for this. Cystic degeneration, as was demonstrated pathologically, has gone on hand in hand with the parathyroid hyperplasia, and

the formation of new hyperactive and hyperplastic tissue is balanced by the fact that some of this functioning tissue has undergone cystic degeneration and become functionless.

We believe in this case that the extent of the kidney damage is permanent, as shown by the fact that the urea nitrogen is still over 80 mgm. Since there is no demonstrable kidney stone by Roentgen ray, or calcification of kidney tissue or tubules, we must assume that this azotemia is due either to calcification of the glomeruli not demonstrable by Roentgen ray, or to fibrosis secondary to the chronic irritation produced by such calcification, resulting in diminished kidney function.

It will be noticed that the serum phosphorus has persistently remained high, despite the fact that the typical hyperparathyroid syndrome presents a high serum calcium but low serum phosphorus.[5] We believe that this high phosphorus is merely another manifestation of impaired kidney function, being part of the marked kidney retention which is shown so definitely by the azotemia present.

Similarly, it is well known that in hyperparathyroidism the urinary calcium is definitely increased, while the fecal calcium remains unchanged. If there is impaired kidney function, however, the urinary calcium remains unchanged, while the fecal calcium may rise. This is described by Churchill and Cope.[6] Thus, in our case, we attribute the normal calcium output both pre-operatively and postoperatively to inability on the part of the kidneys to excrete the calcium, although there was a decrease in the calcium output postoperatively. Unfortunately, facilities for fecal calcium estimation were not available.

Summary. A case of hyperparathyroidism is presented showing azotemia unassociated with hypertension, slight flat bone changes, epulis, and chronic wasting, successfully operated on with removal of a large parathyroid adenoma. The difficulties in diagnosis are presented and discussed. The six diagnostic features of the syndrome are listed in the hope that this condition will be brought to the attention of clinicians, so that future cases will be recognized and brought to operation.

The authors wish to express their appreciation to Dr. Henry Joachim and to Dr. J. J. Guttman for clinical notes and suggestions; and to Dr. Aaron Bodansky of the Hospital for Joint Diseases for assistance with the laboratory determinations.

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PELLAGRA.

An Analysis of Cases Admitted to the Pennsylvania Hospital Since 1922.

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Pellagra, a word derived from a combination of Latin and Greek—meaning "rough or smarting skin"—has been recognized as a disease entity for 200 years. Caspar Casal, a Spanish physician, who first described the disease under the name of "Mal de la Rosa," believed it to be due to dietary and atmospheric conditions. Since 1735 numerous theories have been advanced as to its etiology and the names under which it has been described are legion. Wheeler says, "No other disease has been known by so many aliases." And Roberts feels that "next to lues, Pellagra is the most bizarre of diseases." Its incidence is now known to be very widespread and yet there is little accurate information concerning it. Turner says that "Pellagra is almost unique among major diseases" in this respect.

Of the numerous theories advanced as to the etiology of pellagra from time to time, only two have survived: the infectious and the dietary. Each has its advocates but the evidence points strongly toward the latter as being in some way vitally involved. In 1912, Funk placed pellagra on the list of what he called the "deficiency diseases." These diseases he found could be prevented or cured by the addition to the diet of certain essential food substances which he called "vitamins." McCollum and Kennedy, in 1916, named a "growth promoting and appetite stimulating" factor, "Vitamin B."

Much experimental work has been done on vitamin B, dogs and rats, as well as humans, having chiefly been used. Goldberger and his associates in the United States Public Health Service who did much to clarify the situation, isolated the pellagra preventive factor

(designated the "P. P. factor"). Their belief that it was related to the water-soluble vitamin B has been confirmed in the present recognition of the antineuritic or antiberiberi portion; as vitamin B (B_1 English terminology) and the antipellagric vitamin G (B_2).

Undoubtedly pellagra was present in many localities in the United States prior to its general recognition (Wheeler). In 1864, sporadic cases were reported in New York and Massachusetts. However, the situation in this country was not appreciated until its recognition in Alabama in 1907–1908. Pellagra is especially prevalent in the Southern States, particularly in the "cotton belt" and the mill districts, where it is endemic, and at times epidemic. In these localities, the economic condition of the people is particularly poor. The evil of the "one crop system" (cotton) is reflected in the diet which consists almost wholly of a few non-perishable, comparatively cheap, staple foods of low vitamin content. Endemic pellagra makes up about 98% of all cases and is a disease of poverty.

Sporadic cases of pellagra seen elsewhere in the country are the ones which especially interest us. They make up only about 2% of the total number of cases. Wheeler states that "sporadic pellagra is due to dietary idiosyncrasies and eccentricities, food fads, obsessions, alcoholism, diseases of the gastro-intestinal tract, etc."

Pellagra does not develop until the diet has been restricted for several months—usually 3 to 6. More than 90% of the endemic cases have their onset from April to July and show spontaneous improvement in the autumn and early winter. The disease tends to recur. Most writers feel that it is not contagious or hereditary. Cases have been reported in nursing infants, but it is most commonly seen in children from 2 to 15 years in a mild form. It is more common in women than men. Underhill says, "grief, monotony, disease, constipation, domestic worries, and preparation of food are agents depriving women more than men of their appetites."

The symptoms and signs are many and varied. Bass reminds us that "Pellagra is a systemic disease." Few students forget the chief signs of the "4 D's" "Diarrhea, dermatitis, delirium and death" —an expressive and telling phrase. It is insidious in its onset, as a rule, but cases are seen of a fulminating nature.

To the early symptoms of increasing weakness and lassitude, anorexia, indigestion, sore and ulcerated mouth, diarrhea is usually added. A reduced or absent free hydrochloric acid in the gastric contents is common.

The typical dermatitis usually makes the diagnosis easy. But there are cases of pellagra without dermatitis: the "Pellagra sine Pellagra." Any portion of the skin may be affected: "any form of trauma or irritation may determine the site of the lesions; *e. g.*, radiant energy, chemical stimulus, or physical irritation "(Stannus). The lesions are usually symmetrical and well demarcated. The commonest sites are the exposed surfaces such as the dorsal aspect

of the hands and about the neck (the "necktie of Casal"). The skin becomes red and erythematous, not unlike marked sunburn. Soon pigmentation sets in with thickening, cracking, and fissuring. Secondary infection, blebs and bullæ may be seen, but the "dry type" of dermatitis is much the more common. After desquamation, the skin is pink and shiny in appearance.

The nervous manifestations of pellagra (ranging from paresthesias to marked psychoses), usually occur late in the disease.

The sporadic pellagra seen in this locality is more common than it was one or two decades ago, probably due to prohibition and the economic depression. The rôle of chronic alcoholism and its possible relation to pellagra has been much discussed. Prolonged use of distilled liquors may affect the individual in one of three ways: (1) it may destroy the pellagra-preventive factor; (2) it may interfere with the digestion and assimilation of a proper diet; (3) the appetite may be so reduced that a proper diet is not taken and the individual may exist almost wholly on liquor, usually of inferior grade. Spies and his coworkers believe that cases of pellagra found in the North are usually associated with severe alcoholism. They found that in alcoholic pellagrins the disease was usually curable when large amounts of autoclaved yeast and a full, high caloric diet was taken together with, and in spite of, a daily ingestion of from 600 to 900 cc. of whiskey daily.

On the other hand, in an earlier paper, Spies reports some interesting observations made in a series of 6 typical cases of pellagra. These cases all gave a history of low food intake and 4 of them were chronic alcoholics. They were hospitalized and placed on a carefully controlled diet which was lower in mineral and vitamins C, D, and G content than Goldberger's so-called "pellagra-producing diet." In 5 of the 6 cases, the skin lesions cleared up rapidly. The author writes that "possibly a secondary factor is involved in the production of the disease."

Lesions of the gastro-intestinal tract, interfering with proper nutrition, account for some of the sporadic cases of "pellagra." Ellis feels that any sporadic case which does not respond to proper dietary treatment should be carefully examined from the gastro-intestinal point of view for a pathologic condition which might account for the disease.

The relation of pellagra to Addisonian anemia has been raised. Spies and Payne have proven experimentally that the diseases are distinct. They took the achylic gastric juice from 2 cases of acute pellagra, on a vitamin G-free diet, and incubated it with beef. When this mixture was given to 2 patients suffering from Addisonian anemia, a characteristic reticulocyte response was noted showing the presence of Castle's "intrinsic factor." Absence of characteristic changes in the red blood corpuscles and hemoglobin of pellagrins

with anacidity adds further weight to the assumption that the 2 diseases are of different natures.

For efficient treatment, an early diagnosis is most important. After structural changes have set in, the outlook is much less favorable. A careful and accurate history is especially necessary where cases are seen only sporadically, otherwise the possibility of pellagra will be overlooked. The question of diet must be gone into thoroughly, for the crux of the situation is what the patient actually eats and not what his table or circumstances offer.

Pellagra patients at this hospital are put on a full, high-caloric, high-protein diet, rich in vitamins. To this is added fresh yeast obtained from a brewery in doses of 4 to 6 drams 4 times a day. If diarrhea accompanied by low or absent hydrochloric acid is present, dilute hydrochloric acid in doses of ½ to 1 dram, well diluted in water and taken through a glass tube, is given with the meals. Patients giving a history of chronic alcoholism are allowed alcoholics in gradually reduced doses until the alcohol can safely be eliminated. The skin lesions are treated with a bland ointment unless secondarily infected. The latter, if present, can be cleared with dilute permanganate soaks or wet dressings. If anemia is present and severe, large doses of iron and ammonium citrate (25%) are often given. Liver extract, intramuscularly, also in large doses has been used with good results.

Underhill's experiments with dogs indicate that the addition of vitamin G to the diet is a much better prophylactic than a curative measure. Once the condition of pellagra is well established or advanced, *i. e.*, when structural changes have set in, he feels that hope for a cure is much more remote.

In treating sporadic cases, Roberts feels that encouragement and even psychotherapy are often very important in order to obtain a good result. He adds that the patient must be convinced that his symptoms, such as indigestion, weakness, diarrhea, etc., are caused by the lack of an adequate diet. All too often a patient feels that his troubles are due to the taking of certain foods which are one by one abandoned until the diet is almost completely curtailed, and, instead of improving, the condition becomes steadily aggravated.

The following small series of cases have been observed in the wards of the Pennsylvania Hospital from 1922–1935. In each case, the diagnosis of pellagra was made, and all but 3 have been admitted during the past 2 years.

Case Abstracts. Case 1.—M. R. (No. 6485), a colored female, aged 32, was admitted February 7, 1922. A native of Florida, she came to Philadelphia 2 years prior to admission. She complained of loss of appetite and weakness. Her weakness dated back to an attack of influenza in 1918 and since that time she "had never been herself." She became increasingly weak and nervous and had been bedridden since August, 1921. The appetite became steadily worse and considerable weight was lost. She gave no

history of alcoholism. Her diet, due to economic circumstances, was limited, and considerable corn bread was eaten, but not exclusively.

Examination revealed a markedly toxic and emaciated negress. She was irrational and suffered from delusions. There was marked injection of the mucous membrane of the mouth and pharynx with areas of ulceration. There was a symmetrical, bilateral pigmentation of the malar bones and dorsal surfaces of the hands and wrists.

Laboratory examinations were negative except for a strongly positive blood Wassermann reaction.

A diagnosis of pellagra was made but the patient made little progress and signed her release from the hospital February 23, 1922, unimproved.

Since this patient had only been in Philadelphia for 2 years prior to admission and had been ill during her entire stay, she probably was suffering from pellagra before she came North.

CASE 2.—B. B. (No. 1333), a white male, aged 37, was referred here May 1, 1923 from Snow Hill, N. C., with the diagnosis of pellagra.

The patient complained of "bowel trouble," which he said he had had since he was 10. This and diarrhea were especially severe early in the spring and summer after which they would tend to improve (very suggestive history). The year prior to admission, his condition became much worse and there was no seasonal change. He had been passing 10 to 12 loose, watery stools daily; these nearly always showed a little red blood. The appetite on admission was good, and his diet included eggs, cheese, fish, butter, white bread, soda crackers, biscuits, and some corn bread. He had eaten no vegetables and little meat the year prior to admission because they "upset his digestion." His best weight was 160 in 1911, and on admission he weighed only 100. In 1911, he had some "eczema" on his chest, forehead, and cheeks, which was red and itched some. This eruption was not constantly present, but would come and go. He also contracted the "ground itch" about 1911. About 4 years prior to admission, dermatitis appeared on the backs of his hands, which "comes on especially in spring and when the sunshine is hot." The skin involvement disappeared during the late fall and winter only to return the following spring.

The patient was a farmer. He stated his mother was in an asylum. He also stated that he drank "a little whiskey."

Physical examination revealed a poorly nourished, emaciated white male, who was drowsy. The tongue was smooth and very red. The abdomen was tender throughout. There were numerous, small, discrete, pigmented areas of dermatitis on the exposed dorsal surface of the hands extending to the wrists.

Laboratory examination revealed a marked secondary anemia. Stool specimens were positive for occult blood. Hookworm ova and the *Strongyloides intestinalis* embryo were also present. The urinalysis showed nothing abnormal. The blood Wassermann reaction was negative.

Efforts to control the diarrhea and rid the patient of his intestinal parasites were not successful and he failed steadily. He died, after being irrational for 2 days, July 19, 1923.

CASE 3.—V. B. (No. 7748), a colored female, aged 29, a native of Florida, who had lived an unknown period in the North, was admitted to the wards on 3 occasions from October 25, 1928, to February 25, 1933. Between admissions she was followed in the Outpatient Department.

Her chief complaint was constipation, first noticed in 1924. She got along fairly well until 1927 when she had to resort to purgatives in order to obtain soft, watery stools. On her first admission (1928), her bowels would only move after purgation and straining, accompanied by a sense of constriction in the anal region. Her appetite was good but she was "afraid to eat on account of difficulty in moving the bowels."

Physical examination at first was negative, except for a stricture of the rectum about 1½ inches proximal to the sphincter. This was dilated under general anesthesia and the patient was shortly discharged, greatly relieved.

She was readmitted January 11, 1933, with the same complaints and diagnosis. The interval history stated she had been well following her discharge in 1928 until 1930 when the old symptoms returned. She suffered increasing weakness, loss of weight, chills and fever and progressive constipation, with all stools containing blood, mucus and pus. She had lost considerable weight, and her blood count showed 30% hemoglobin and 2,600,000 red blood cells. The skin was dry and dehydrated but as yet showed no lesions. Dilation of the stricture was again resorted to. The Frei test for lymphogranuloma inguinale was suspiciously positive. She was discharged to the Outpatient Department, improved, January 28, 1933.

Her final admission came only one month later, February 25, 1933. She had become much worse and her emaciation and dehydration were marked.

She was transferred to the Medical Ward March 17, 1933, when a symmetrical, dry, pigmented dermatitis, extending up to the wrist, was noted on the dorsal surface of the hands. Later, similar skin changes were noted at the elbows. Her course was progressively worse and 1 week prior to death, the patient became demented.

Laboratory Data. Blood Wassermann test negative. Marked secondary anemia. Volume index, 0.77. Fractional gastric analysis showed a normal amount of free hydrochloric acid. The urine showed 1+ albumin and an occasional hyalin cast.

At autopsy (Dr. J. S. Taylor, 3 hours after death), the following conditions were found: (1) pellagra; (2) extensive ulcerative colitis involving the descending colon, sigmoid and rectum with fibrosis and narrowing of the lumen for the distal 7 to 8 cm. with stricture formation; (3) acute purulent peritonitis.

This case is the most unusual and interesting of the series. Pellagra developed secondarily to a lesion of the gastro-intestinal tract, which markedly affected nutrition and digestion. The lesion was a rectal stricture caused by lymphogranuloma inguinale.

CASE 4.—M. M. (No. 31059), a white woman, aged 54, native of Philadelphia, was admitted July 16, 1934, complaining of fatigue and nervousness, with pigmentation of the backs of the hands and anterior portion of the neck and chest. Her appetite had been very poor for 2 or 3 months prior to admission and she had eaten a lot of candy. Three days prior to admission, after washing clothes, she noticed that the backs of her hands were pigmented and somewhat painful. She attributed this to the use of laundry soap (the same brand which she always used) and the effect of sunlight. The skin of the neck and chest became involved at the same time. The involved area "burned" her.

Her bowels moved 2 or 3 times daily. There was no diarrhea and only occasional indigestion. Her diet, prior to admission, had been reduced, due to poverty and for sometime she had lived chiefly on bread, butter, tea and coffee. She gave no history of alcoholism.

Physical examination revealed a faint, reddish-brown pigmentation over the malar bones. The tongue and lips were very red. There was an area about the size of the palm of the hand on the anterior chest below the clavicles and the suprasternal notch which was reddened, desquamated, and indurated. Over the entire dorsum of the hands extending just above the wrists was a brownish-red, desquamating pigmentation of the skin. the ankles were also pigmented.

Laboratory Findings. Urine, normal. Blood Wassermann test negative. There was no anemia. Free hydrochloric acid was present in the gastric contents. Serum protein was 5.6%.

Under treatment, the patient improved rapidly and was discharged October 6, 1934.

CASE 5.—L. S. (No. 33137), a colored female, aged 36, native of California who had resided in Philadelphia for an unknown period, was admitted to the Ward, January 15, 1934, complaining of weakness, diarrhea, dermatitis and an abdominal mass.

Her diet, for a year prior to admission had consisted almost entirely of bread, soups, and cereals. Her appetite began to fail in November, 1933, and she felt increasingly tired and listless. This was followed by soreness of the mouth and a burning sensation of the hands, plus the appearance of dermatitis on the dorsal surface. One week prior to admission, diarrhea set in. There is no history of alcoholism.

Physical examination revealed pigmented areas, almost black, with cracking and fissuring on the backs of the hands and wrists. Similar areas were present on the dorsal surface of the feet and about the genitalia. The tongue was markedly reddened with whitish plaques on the dorsum and about the frenum. The uterus contained several fibroid tumors.

Laboratory Findings. There was a moderate secondary anemia. Urine, normal. Blood Wassermann test negative. Free hydrochloric acid was present, but reduced, in the gastric contents. The stools were positive for blood.

In spite of the usual treatment, the patient became steadily worse, and died January 30, 1934.

AUTOPSY (Dr. A. D. Wallis, 3 days after death). A few of the findings are presented: "A scaly dermatitis was noted at the angles of the mouth and on the dorsum of the hands including the fingers and a short distance beyond the thenar surfaces of the wrists. This was deep brown, almost black, with moderate scaling, and areas of bleeding ulcers. Microscopically, the papillæ projected downward, deeper than usual, and pigment production of the lower layers was definitely increased. Round-cell infiltration was scattered throughout the upper layers of the corium and as deep in places as the subcutaneous tissues. Nothing except a moderate amount of cortical atrophy was noted in the brain. Death was probably due to pellagra.

Pathologic Diagnosis. (1) Pellagra; (2) multiple leiomyomata uteri; (3) old chronic bilateral salpingitis.

CASE 6.—J. H. (No. 34662), a white male, aged 54, native of Philadelphia, was admitted June 1, 1934, complaining of burning of the backs of the hands of 12 days' duration. Six years prior to admission, following a prolonged diet consisting chiefly of "stews" and no vegetables, the patient developed a dermatitis on the dorsal aspect of the hands and suffered from diarrhea. He was told he had pellagra and was followed in the Outpatient Department of the Hospital. In 6 months, he had apparently completely recovered with treatment and an improved diet. He had been well until 12 days prior to admission when the diarrhea and dermatitis reappeared. The patient had been unemployed for 2 years and his diet for 6 months before admission consisted chiefly of pork and potatoes, plus a heavy and consistent consumption of alcoholics of a poor grade.

Physical Examination. The patient's mental state was active. There were widespread ulcerated patches of pigmented skin on the dorsal surfaces of the hands up to the wrists.

Laboratory Findings. Urine showed 1+ albumin. There was no anemia. Fractional gastric analyses showed achlorhydria. The blood Wassermann reaction was negative.

The patient showed rapid improvement upon withdrawal of alcohol and bettering the diet and nutrition with the usual methods mentioned. He was discharged June 18, 1934.

CASE 7.—L. E. (No. 34839), a colored female, aged 31, native of North Carolina, whose stay in Philadelphia is not known, was admitted June 18, 1934, complaining of pain in the chest, fever, sore mouth, and loss of appetite with dermatitis of the hands. The history was indefinite as to the duration of the loss of appetite and the presence of dermatitis, but for several months the patient had consumed large amounts of alcoholics and eaten very little.

Physical Examination. The tongue and pharynx were very red. There was desquamation and hyperpigmentation on the backs of the hands and wrists. No changes were noted over the neck, feet, or genitalia.

Laboratory Findings. Urine, normal. Blood Wassermann test negative. There was a slight secondary anemia. Gastric analysis showed no free hydrochloric acid.

The patient made an uneventful recovery upon the withdrawal of alcohol and the substitution of proper diet and treatment.

CASE 8.—D. D. (No. 35068), a colored male, aged 77, native of Philadelphia, was admitted July 8, 1934, complaining of vomiting, diarrhea, and itching of the skin. He was very poor, and had no one to care for him. For several months prior to admission, he had lived on cereals and rice chiefly. He had suffered from pruritus for 3 months before entering the hospital, but the vomiting and diarrhea were only of a few days' duration. There was no history of alcoholism.

Physical Examination showed areas of rough, desquamating hyperpigmentation on the dorsal surface of the hands and wrists, also over both ankles. It is of interest that the patient attributed his dermatitis to sunburn.

Laboratory Findings. Urinalysis showed 1+ albumin with an occasional cast and red blood cell. There was a slight secondary anemia. The blood Wassermann test was negative. Fractional gastric analysis showed a hypochlorhydria.

CASE 9.—S. P. (No. 35456), a white male, aged 48, native of Philadelphia, was admitted August 17, 1934, complaining of weakness, loss of appetite, and failing vision. He was in good health until 4 months prior to admission when he began to drink heavily and steadily. He consumed from 1 to 3 pints of cheap whiskey daily and began to suffer from increasing weakness, loss of appetite, and failing vision. One month before admission he noted redness and roughness of the backs of his hands and he passed 6 to 7 watery stools daily.

There was a loss of 40 pounds in 4 months, and the patient stated he had eaten more during his first 3 meals in the hospital than he had during that entire period. The patient was a mattress maker, unemployed for 9 months. He had only occasionally partaken of alcoholics previously.

Physical Examination showed rather marked emaciation. On the dorsal surface of each hand, extending up to the wrist, was a rough, scaly, symmetrical, pigmented dermatitis.

Laboratory Findings. Urine, normal. There was a mild secondary anemia. The blood Wassermann test was negative. Gastric analysis showed an achlorhydria.

Under treatment there was a progressive clearing up of the diarrhea and dermatitis. It was thought that the patient had an alcoholic neuritis of the legs as he complained of tenderness along the nerve trunks. After considerable rest, baking and massage were instigated; and the patient was discharged, much improved, to a convalescent home, October 18, 1934.

CASE 10.—W. J. (No. 36722), a colored male, aged 28, native of North Carolina, had been in Philadelphia 7 years before admission. He entered the ward, December 30, 1934, complaining of pain and tenderness in the soles of his feet, diarrhea, and abdominal distress. He had been perfectly well

until 3 months prior to admission when he began to suffer from weakness, loss of appetite, and paresthesias of his feet. His bowels moved 3 times a day and he felt dull and apathetic. Three weeks before admission, the patient began to suffer from diarrhea and abdominal distress. There were 15 stools daily; and at times, tenesmus was present. At this time, the patient noticed a dry, scaling, atrophic dermatitis on the backs of his hands and wrists and also about the ankles.

He gave a history of having consumed a pint of cheap whiskey daily for a period of 18 months to 2 years with a corresponding reduction of diet. His diet consisted chiefly of a small amount of canned meat and vegetables with occasionally fresh fruit.

Physical Examination showed a mentally dull, young, colored male, lying flat in bed. He was dehydrated and had a slight odor of acetone on the breath. There was oral sepsis, and the pharynx was diffusely injected. Glossitis was present with atrophy of the papillæ and tremor. There was a dry, scaling, pigmented dermatitis on the dorsal surface of the hands, extending up to and including the wrists. The skin was desquamating in thin sheets. There was hyperpigmentation over the malleoli and dorsal aspect of the feet with desquamation. The anterior surface of the neck and chest showed hyperpigmentation, but the distribution was not that of the typical "necktie of Casal."

Laboratory Tests. Urine, normal. Blood Wassermann test strongly positive. Stools, moderately positive for blood. No anemia was present, but 16,800 white blood cells were found.

The patient is still in the ward, but has made a gradual progressive recovery, and is soon to be discharged.

Discussion. Although pellagra has been known for 200 years, it has not been until the past three decades that its presence and seriousness in the United States has been given much attention. The disease is a serious one. Wheeler reports that in 1930, there were 7146 deaths from pellagra in this country, and that for each death 35 persons were disabled.

Pellagra is endemic in the South and its presence in that locality is far more common than in the North. In spite of an increase in the incidence of the disease in recent years, the author believes that many cases in the North are overlooked. Like syphilis, pellagra is a bizarre disease. Medical schools teach us to be "syphilis-conscious" —we should also be "pellagra-conscious." The classical case is recognized by any physician, but pellagra often does not make a classical appearance. We are too prone to think of the condition as only affecting the dermal, gastro-intestinal, and nervous systems —forgetting that the disease is systemic.

For years the etiology of pellagra has been argued and the point has never been definitely settled in spite of a great deal of experimental work. Dietary deficiency *versus* infection is still a moot question.

Pellagra is primarily a disease of poverty and ignorance. However, members of the more well-to-do classes of society are not immune and frequently, have some very strange ideas about the question of diet. A careful history in obscure cases is essential.

The important thing to learn is what the patient under observation actually eats and not what his table or circumstances offer.

Pellagra is an insidious disease in most instances. It tends to be seasonal, to recur, and to show remissions. The physician should be alert for its appearance, or cases are sure to be overlooked.

All of our cases seen at the Pennsylvania Hospital since 1922 have been ward admissions.

Case 1 is a case of Southern endemic pellagra, who had been ill during her 2 years in Philadelphia. Unfortunately after 16 days' hospitalization, she left unimproved.

Case 2, also was a Southern endemic case. His pellagra was complicated by infestation with hookworm and strongyloides intestinalis. Nothing could be done for this patient whose condition, when seen, was advanced; and he succumbed.

Case 3, to me, is the most interesting one of the series. The patient suffered for 10 years from a rectal stricture which had to be dilated, under general anesthesia, on 2 occasions. The stricture was secondary to lymphogranuloma inguinale. Not until shortly before death did symptoms of pellagra appear. The patient had gradually reduced her diet and resorted to more purgation in order to keep her intestinal canal open.

Cases 4, 5, and 8 developed pellagra secondarily to diets wholly inadequate as to vitamin content, taken over a long period of time because of poverty. Cases 6, 7, 9 and 10 developed the disease after existing over considerable periods on liquor of poor grade with a simultaneous marked reduction of proper food.

Summary. Ten cases of pellagra seen on the wards of the Pennsylvania Hospital since 1922 have been reviewed and discussed. All but 2 were admitted during the past 2 years. The author feels that there has been a real, rather than an apparent, increase of pellagra in the North during recent years. Prohibition, with its attending increase in inferior grades of alcohol, and the economic depression are believed to be causative factors.

Of the 10 cases reviewed, 2 had developed pellagra in the South where the disease is endemic. Of the remaining 8 sporadic cases, all seen during the past 2 years, 4 were native Philadelphians, 1 had lived in this city for 7 years, and the duration of residence of 3 is unknown.

Prolonged restriction of food intake, due to poverty, was the etiologic factor in 5 of the cases. The disease developed following chronic alcoholism in 4 cases, and secondarily to a gastro-intestinal lesion in 1 case. Autopsies on 2 of the 3 fatal cases are presented.

Pellagra, as it often does not present the characteristic picture, may require great diagnostic acumen. A carefully detailed history, especially as to amount and kind of food actually eaten, is essential. The condition has become more common in the North in recent years but it is felt that obscure cases are frequently overlooked.

It is hoped that physicians will become more pellagra-conscious and attack the menace early before the disabling structural changes have set in.

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THE PSYCHOLOGIC BACKGROUND OF COLITIS.*

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One of the ideas I do want to put forward is that ulcerative colitis may be the end result or organic consequence of functional disorder of the colon. Let me give you an analogy: The late Dr. Crookshank[1] used to classify angina into three types: (1) The false or hysterical: 95% functional and 5% organ inferiority. (2) The more severe: 33% poisoning, 33% functional, 33% over-

* Read to the Medical Society of Individual Psychology, December, 1934.

strain of cardiac muscle. (3) Angina gravior: 5% functional, 95% gross disease. I believe that colitis by analogy can be classified in a similar fashion into functional, intermediate and ulcerative. (The *Lancet* speaks of colitis gravis.[2])

Much research has been carried out into causes of ulcerative colitis and much bacteriologic ingenuity has been exercised in order to incriminate this or that particular coccus without very convincing results.[3] Surely what has been overlooked is that with the few exceptions of fulminating infection,[4,5] the ulcerative stage is a terminal condition and the infection would not have taken place except in a colon already disorganized by repeated dysfunction.

We must realize that to speak of curing a patient of ulcerative colitis is to make a claim as unreasonably impossible as to speak of curing coronary thrombosis or malignant hypertension. Jones[6] only claims 10% of cures. The truth is that such patients are incurable. Gross organic changes have taken place in the mucosa of the bowel, in the myocardium, in the elastic tissue of the arteries and palliation is the most that one can expect. But prevention of these terminal states can be attained if the functional disorder is recognized in good time and as partly an expression of an emotional state.

What I hope to do is to illustrate the stages by which the patient and his or her colon graduates in despair and degeneration from functional disability to gross organic lesions. We must bear constantly in mind that the patient cannot be separated from her colon, or the emotional state from the somatic symptom.

It will be useful to introduce another analogy at this stage. When faced with a case of sexual impotence or ejaculatio precox, we do not rush at the patient with a urethroscope to examine the verumontanum or inject his vesiculæ seminales with lipiodol.[7] There is, of course, a type of mind which holds that seeing is believing and such procedures are still carried out in certain quarters. But most of us here I think would begin by attempting to assess the patient's attitude to sexual function as a more useful approach to the problem. In like manner I would suggest that in dealing with a patient reporting symptoms of dysfunction of the colon the case investigation is incomplete if the physician has failed to ascertain the patient's attitude to bowel function. The objective physician may smile at this invitation to the patient to give free rein to his fancies, but I do maintain that useful information is lost by not taking advantage of this subjective approach. For such an attitude does exist, of course, and one has only to read the advertisements in the daily press or even the reputable scientific journals to realize that some of the manufacturers of laxatives and aperients deliberately cultivate this attitude of mind.

You must have noticed the general tendency in these advertisements to project on to the large bowel the ideas of impurity, of bad

habits, of sluggishness. As children our "nannies" used to tell us when we were in sulky moods that there was a little black man on our shoulders. Now the aperient mongers try to convince us that all our depressions, lassitudes, lazinesses are due to the big black tube inside us. But as we agree that regression may play a big part in determining the nature of our illnesses, it may be useful for a few minutes to analyze the way in which we are instructed to regard bowel function. I do not propose to be subtle, or Freudian, about this, or to talk about anal erotism, but rather to present to the actual sequence of events.

The first impression, I suppose, of a breast-fed baby after an action of the bowels is that he feels very uncomfortable. He calls for assistance—his cries are generally effective and bring his mother or nurse on the scene. And so we have defecation—discomfort—call for help—mother. And I think there is some evidence that, like Pawlow's dogs, who salivated at the sight of food when the bell was ringing, and later were conditioned to the bell, so, in some infants, at any rate, an association is established, making defecation a call for help or attention.

The other conditioned reflex which may be established in infancy is the emptying of the bowel which takes place when the infant is frightened. One pediatrician claims that a great deal of the diarrhea in children's wards in hospital is not infective at all, but is a fear reaction, due to frequent handling by strangers. He claims that the small infant, handled by a probationer rather than its mother, and constantly disturbed with unfamiliar rites, such as temperature-taking and physicians' examinations, is likely to empty its bowels frequently, and such diarrhea can be eliminated by a picked staff of nurses infrequently changed who handle the infants carefully and economically.

The next psychologic factor in the development of bowel function is that invoked in the training of the infant to a regular reflex. This is practically the first demand made by Society—through the mother or nurse on the infant. The child soon learns that if it delivers the goods it receives encouragement—that if it fails to respond, displeasure, even annoyance may be exhibited by its guardian. And so it finds that by its bowel function it can provoke varying emotions from its personal environment.

It has discovered a new channel for exercising power. Quite apart from question of diet, many cases of constipation in children over 6 months old exhibit this factor of purpose. The infant can realize its power of attracting attention by refusing to comply with the demands of Society. And some of the cases of incontinence of feces are the end result of this particular practice.

Case Reports. CASE 1.—A bright child, aged 3 years, was the younger sister of an epileptic boy whose mother was devoted to him and spent all her time and care on the boy, rather to the neglect of the daughter. The

daughter's response to this situation was constipation which had the desired effect of focusing the mother's anxious attention on her. The defecation stimulus was neglected to such a degree that it was only by voluntary effort that the stool was retained. But when the child's attention was diverted at play, a stool was often involuntarily passed, whereupon she would burst into tears of rage and vexation. Here the rectum, under the influence of emotion, is being trained, as Schilder[16] would say, in a pathologic direction.

And this brings us to the point where moral factors are introduced. The baby is told she is a good girl when she obliges with a stool at the correct time, and not uncommonly that she is "bad" when the pot is found to be empty.

It is, to say the least, significant that the first notions of goodness and badness, or good and evil, are associated in the child's mind with the production of a stool. That this association does persist into adult life is quite evident to me. Numbers of patients come to me because of alleged constipation. Often, as Hardy[8] points out, Roentgen ray examination reveals an accelerated passage of barium through the bowel in a patient who has been taking purgatives daily for relief.

Case 2.—A married woman, aged 43, complained of constipation. She was brought up by a very strict mother who incidentally was not so strict with a younger sister, and was "her father's girl." (She says her father was constipated.) As a baby she had colic and screaming attacks, and was constipated when at school, at the factory, and since marriage. Her mother gave her senna and castor oil regularly. Her happiest time was at the factory, but before she was 19 she was kept at home by her parents, as her mother was pregnant with her youngest sister and the patient had all the nursing to do.

She married 10 years later, but not happily. A miscarriage followed after 3 years, and since that date no pregnancy has occurred. Last year she went back to live with her parents. She still feels her youngest sister is the favorite. She complained of many abdominal discomforts which she rationalized as due to the "constipation;" but a barium meal showed that the meal was hurried out of the stomach and was in the rectum in less than 6 hours. I feel that the imagined constipation in this case was a protest against the strict mother's favoritism.

Case 3.—Another conscientious clerk consulted me for constipation, for which he had taken purgatives for years, and prescribed for himself a diet which drove his wife almost distracted (surely a purpose there). He was outraged when I suggested to him that he leave off his aperients. He could hardly have been more shocked if I had recommended him to seek extramarital intercourse. It was quite obviously a moral question with him and his rather rigid mind had grown up to think that it was wrong to be constipated and he disapproved strongly of my advice to allow evil that good might come. Such people are like those Pharisees without understanding, who still believe the tradition of the Elders. For them the text obviously runs "out of the colon proceed evil thoughts, murders, adulteries, fornication, thefts, false witness, blasphemies," etc., and to such people I reply by telling them of the patient I had in hospital.

Case 4.—The patient was a case of anorexia nervosa, and admittedly her food intake was small. Aperients and enemata I considered contraindicated and, as she was under observation in hospital, I allowed her to go 16 days

without a stool. During that time she had no headache or marked distention, and on the 17th day had a natural action and followed this up by establishing a rhythm of natural defecation every third day. Roentgen rays showed that she was not a case of Hirchsprung's disease.

While in some cases the trouble originates in the child demanding more attention from the parent, in others it is the parent who is responsible for determining an emotional association. Over and over again we all hear in the outpatient departments: "Do you have to give the child opening medicine?" "Oh, yes, I give him syrup of figs every Saturday." "Why? Does the child miss an action of the bowels on Friday?" "Oh, no, Sir, but I thought I ought to." Here again we have this notion of right and wrong; this time in the parents' mind. It would be wrong to let our Ernest get constipated, and so Ernest after suffering the weekly ablutions externally, also suffers internal pangs of purification on Saturday night, and thus is brought up to believe *qu'il faut souffrir pour être pur*. A weekly punishment is inexorably demanded, and he can only avoid this by diarrhea.

This fuss and bother about constipation as if it were a crime is well illustrated by the following case:

Case 5.—Two years ago a mother brought her daughter, aged 18, to my outpatient department for the most obstinate constipation. The girl looked pale and atonic and complained of backache, which she stated was worse after stool (a protest against defecation?). A skiagram of the lumbar spine and pelvis was negative. Rectal examination was negative. The mother told me that she herself had phthisis and could do no housework, so that her daughter looked after the household, of father, invalid mother, 4 brothers and a younger sister. The mother was evidently very obsessed about the constipation, and the girl told me subsequently that the whole family were concerned over the action of her bowels, and that it was a matter of diurnal inquiry by each and every member of the household. When she came to see me, she had already lost her appendix at 15 and her coccyx at 16 in the quest of a cure. From the bullying manner of her mother, who now demanded a colectomy, I strongly suspect the wretched family physician had arranged these previous operations in self-defense. The girl, of course, had not improved as a result of these mutilations. Her mother told me that her daughter was not inclined to go outdoors, had no interest in boys and her sole amusement was in the activities of the local parish church. Her mother said she was good tempered, and did not grumble. I thought her sullen. Roentgen rays showed normal progress until the colon was reached; then some delay; a partial evacuation at 72 hours and great distention of the rectum with final evacuation after 110 hours. The descending colon showed excessive haustration. I think this girl had certainly acquiesced with the domineering diagnosis, just as she had accepted without enthusiasm the rôle of household drudge. Her interesting complaint which defied all doctors served as an introduction to various hospitals, where she lay uncomplaining for a few weeks each year while her malady was investigated.

I learned recently that this struggle had a further sequel. The mother, insisting that this constipation must be cured, persuaded a fresh surgeon to do a sympathectomy. The daughter, passively resisting, "I won't be cured," survived the sympathectomy without any alteration to the con-

stipation much to the surgeon's chagrin, and the mother, who still refused to acknowledge defeat, roundly abused the surgeon for his unsatisfactory intervention.

It is not difficult to foresee the organic end result in this case. I believe this patient with her enormous dilated rectum, which practically fills the pelvis, will ultimately develop into one of those cases of dolicho colon, and each loop will make the mass reflex more difficult. The bowel will become more overloaded. Fresh flexures will develop until the picture of redundant colon is fully developed.

This curious childish submission to the maternal diagnosis was again illustrated in another case of "colitis." The last patient had not become adult enough to be interested, or at any rate to admit her interest, in boys.

CASE 6.—This patient, a woman aged 33, had got as far as getting engaged. She had, however engaged herself to a fiancé of whom her widowed mother and army brother most strongly disapproved. In fact, the patient must have had some doubts herself, for every time he came to visit her, even when she was away from the family at a convalescent home, she felt "sick" and she passed loose motions.

She had been sent into my ward with a diagnosis of tuberculous peritonitis, which had been hailed with satisfaction by her brother, who, on learning the diagnosis, told the fiancé that his sister would be an invalid for the rest of her life, and the engagement must be broken off. Her early history was that she had always got on better with her father than her mother. Her father died of a duodenal ulcer when she was 14. She said that hit her very hard. Her mother was very affectionate and demonstrative, but there was always friction at any manifestation of her daughter's independence; she would not admit that either daughter or son had grown up.

When she was 20 her mother's nerves became very bad. The patient woke up one night with abdominal pain and vomiting. Appendicitis was diagnosed. The mother and family doctor were nervous and wanted to be on the safe side, so she was sent away for a seaside holiday.

She improved until the day after her return to home, when she had another attack of pain. The appendix was removed, but the incision took a long time to heal up; there was no sepsis. The skin flaps failed to unite. For the next 2 years she was treated as an invalid, and it was only at the age of 24 that she began a belated training as a teacher. She met her fiancé, a worthy but impecunious young man, when she was 32, and became engaged almost at once, but put off announcing the dread fact to her family for 6 months. Then the storm broke. The brother, an officer in a famous regiment, was horrified; he claimed he should have known about it before, and in his best parade ground manner told his would-be brother-in-law that he was a cad. Her mother insisted that if she persisted in marrying this man the family would have to keep him.

Two months of these family rows had their effect, and one morning my patient fainted in her bath. She was put to bed, and when she got up again she noticed a dragging pain at the appendicectomy scar. Each day for a week she rose from her bed and promptly subsided in a faint. The family doctor was called in. Roentgen rays were advised. Some calcified glands were found in the abdomen. A 4-hourly temperature chart showed some fever, and there was the diagnosis of tuberculous peritonitis. But I found that mental excitement had always sent her temperature up and brought on loose actions of the bowels ever since she was a little girl. When she was sent to my wards she had accepted the rôle of the incurable

invalid, and was quite upset when I questioned the diagnosis. For that involved taking up the struggle again, coping with disapproving mother and brother and marrying her fiancé. But I was able to demonstrate her flight into illness to her satisfaction, and I was pleased, a year later, to receive a grateful letter of thanks, stating that she was happily married.

I have another example of a widow—only daughter situation.

CASE 7.—This was a girl, aged 20. Her father had died when she was 5. She was the middle child, the other 2 children being brothers. She had always suffered from stomachache when frightened. Apart from her bereavement, she had experienced an uneventful childhood. She took a little time to settle down at school under a strict headmistress, and became a typist at 16. She dropped athletics on leaving school. She would have liked to play tennis, but could not afford it. She found officework uncongenial and grumbled at having to earn her living. On her holidays she stayed at home reading a book. She had very few friends, girls or boys. When she was 19 she had some hemorrhage from the rectum, and was treated for hemorrhoids. Later she suffered abdominal pain and began to pass mucus. After 2 months in bed, she was admitted to one of the teaching hospitals and sigmoidoscoped. Nothing was found except a mucous membrane studded with small bleeding points. She recovered after a seaside holiday, and went back to work for 9 months, and then relapsed.

After another 2 months of passing blood and mucus, she was admitted to my wards. I found her very controlled and unemotional. She was not in the least worried about her illness, and stoically put up with the abdominal pain, behaving like a well-brought-up child. I could not elicit any admission of worry or distress. She owned she was bored with her job and the family poverty. A skiagram showed complete loss of haustration of the colon. Not a single sacculation was to be seen from end to end. After six weeks in hospital she improved very considerably, and some days passed without any discharge from the rectum.

Rather significantly, on learning that she was to be discharged, the stools rather rapidly increased again.

This girl had been brought up in a fatherless household, by a woman of considerable personality. Although very attractive in a rather babyish way, she was significantly lacking in the natural interests of youth. She had made no effort to cope with sex, or society, and had retreated from the problem of earning a living. The increase of diarrhea before leaving seemed to hint at a reluctance to return to the rather overpowering influence of her strong-minded mother.

CASE 8.—My next patient had gone rather farther than the last case, for not only had she found a boy friend, but she had permitted matters to progress so far that she had become a mother. This was unfortunate, as she had dispensed with the preliminary legal formalities. However, she was carrying on the family tradition, as she had been brought up in an institution for foundlings, and had never known her mother. Not very intelligent, she had not recognized her condition for some months, but soon after discovering what was the matter she began to pass blood and mucus per rectum. No characteristic organisms were recovered and she was admitted to hospital; the "colitis" cleared up after parturition. I was allowed to investigate her case history by the courtesy of Dr. Phillips, of the Southmead Municipal Hospital. She was suspicious and I was unable to win her confidence, so that I was unable to discover much about her early

background, except that life in the institution had been pretty grim. As the "colitis" persisted after admission, I think the possibility of the self-administration of abortifacients can be excluded.

I have another case of "colitis" in pregnancy in my hospital file:

CASE 9.—A married woman, aged 23, a small, fluffy blonde, whom newspaper reporters could hardly avoid describing as a girl bride. She was the youngest of 7 children. Her father died when she was 13. Another widowed mother. Her mother, she remembered, use to dose her with syrup of figs as a child. On leaving school she became a maid at a boarding house and married the visiting milkman at 19. They lived at first in rooms near her mother, but 2 years later the milkman bettered himself and installed his wife in a brand new Council house in a garden suburb some miles away from his mother-in-law. Within a few months of the separation my patient developed pain, sickness and diarrhea. This illness invalided her for 9 months, and had the much desired result of bringing her mother to the rescue, ostensibly to do the housekeeping. She recovered, and all went smoothly for 9 months. Then a relapse set in. She was admitted to my ward 2 months later, and I found on examination that she was 3 months pregnant. I also discovered that she had not told her husband or her mother of the amenorrhea; further, that she was scared stiff about the pregnancy, having heard some realistic descriptions of labor from her young married acquaintance. She began to improve after reassurance, but unfortunately I dieted her rather strictly, as vegetables and fruit increased the secretion of mucus. She developed a pellagra-like condition, with pigmentation, pustular rash, stomatitis and paresthesias. Wallwork, in a discussion at the Cabot Clinic, described a similar sequel during the treatment of a case of ulcerative colitis. She could not tolerate bemax or marmite, and before I could give her more than one dose of liver as a source of vitamin B she aborted. After the miscarriage she rapidly improved.

And now I want to describe another type of case which I think of as the "rolling stone." More accurately, I am thinking of the middle-aged spinster who has never been trained to earn her living, and who, as Barber said of a case of mucous colitis, "remained at home a failure."

CASE 10.—One example I dealt with recently was a lady, aged 57. Since the age of 17 she had always been subject to "attacks" of diarrhea when she was preparing for any special occasion. She started work as a milliner. She had to take it up, she said, but she loathed it, and at the end of 5 years she developed "colitis" and retired from the commercial struggle. Eight years later she was still hoping for a cure, and underwent a curettage, believing she would get some relief. Two years later she was admitted to a London hospital for observation and was discharged with the information that her case was incurable. Having no means of her own, and 4 brothers, all married with young families to support, she attached herself to a wealthy but delicate cousin as a companion, and for 20 years she maintained a roof over her head by adapting herself to the whims of a semi-invalid. This tyrannical old lady did not permit her companion to leave her even when her mother was seriously ill, but graciously extended her a day's leave to go up for the funeral.

Even this bereavement did not provoke a diarrhea, but 9 months later the rich employer had to enter a nursing home for a serious operation. The prognosis of the surgeon was very grave, and so my patient was at last brought face to face with the precarious reality of her existence and

suddenly collapsed with sickness and diarrhea. When admitted, her chief phobia was that the other patients in the ward were going to die, an obvious projection of her terror that her protector was about to perish. She told me that she felt abandoned, that she had no claim on anybody. She made little improvement until the news came that her cousin had survived the operation, had sold her house, and was going to live abroad, and her services, such as they were, would no longer be needed. Her last hope gone, my patient found that when the worst came to the worst, she could face it, and 2 days later she discharged herself, much improved and ready to tackle the world.

CASE 11.—Another patient, aged 66, was the middle child in a family of 5. Always delicate, she never ran about like other children, and was allowed special delicacies on account of her weak stomach. At the age of 17 she developed "colitis" while she was waiting for admission for an operation for strabismus, and passed blood and mucus. She was trained for book-keeping, but she did not like it, and at the end of 5 years gave it up on the pretext that she had to prepare for her marriage which took place a year later. After being married for 20 years her husband left her. Her younger daughter departed to keep house for her father, her elder daughter was married by this time and living in Singapore. Once more she was alone in the great big world; and so she settled down for the next 16 years to a life in London bed-sitting-room, doing unskilled nursing. She gave up this hand-to-mouth existence 4 years ago to come to Bristol to nurse a dying sister. The sister died after 9 weeks and for the next 4 years the patient continued to bolt in and out of boarding houses and convalescent homes wangled from her panel doctors. Having left the metropolitan scene of her labors, she lost her connection, and there was no demand for her services as unskilled nurse in a strange city, and finally when she was sent to me, she had come to the end of her money and resources. She had stayed with all her friends, been to 3 convalescent homes in as many months, and now the "colitis" had begun again. On admission she was Roentgen rayed; the barium meal reached the cecum in good time, but did not progress further than the ascending colon for 48 hours and reached the transverse colon in 96. There was no ptosis but a little diverticulitis. She subsequently survived 10 days without an action of the bowels, without rise of temperature or discomfort. With a technique borne of years of practice she mobilized the good will of the almoner and on discharge had found herself yet another temporary perch.

My last case is another example of the widowed mother-daughter situation:

CASE 12.—The patient was the youngest of a family of 3 girls. The father had died when she was young. This girl was the brains of the family, who saw to it that these were duly exploited. As a librarian, she kept the rest of the family, and was expected, after long hours, to come home and do the greater part of the housework. The mother was perfectly healthy, but the most selfish woman I have ever heard of. I learned nothing of this from the patient, but from her doctor. For 10 years she was the family Cinderella. Then she developed appendicitis, and was operated upon for a perforated appendix. Once the treadmill of service ceased to revolve, it was difficult to start again. The patient made a slow recovery, keeping to her bed for 5 months. She was never able to resume her work, but stayed at home to listen to the interminable regrets of her mother for the days when the family were better off on her salary. The family, anxious to conserve the source of the golden eggs, sent her to this doctor and that in a hope of getting her back to work again, and eventually an enthusiastic surgeon discovered an alleged septic focus in her tonsils and these were

removed. But their hopes were dashed; she developed "colitis." Roentgen rays showed ulceration of the colon; the stools a non-lactose fermenter, and in 8 months she slowly slipped down hill, in spite of blood transfusions, and died. Her mother characteristically kept away from her deathbed, as she found these scenes so "trying."

I have tried to convey to you this short series of cases the psychologic background of "colitis," as I have seen it. The President[10] has already described a case in his paper and C. D. Murray,[11] in America, has also published a short article on this question.

I think we can claim that many of these cases begin as an alteration in function of the vegetative nervous system, which selects the colon as the battlefield on which the emotional conflict is fought out. As 1 patient of Bockus[12] said: "The amount of mucus in my bowel is a barometer of my nervous state." I have never been able to satisfy myself in my own cases that there was any organ inferiority in bowels. Many of my patients had a normal bowel without ptosis or kinks, or redundant folds.

Perhaps it is as Larionov,[13] the Russian artist, said of some paintings produced by artists when serving their term of conscription in the army, "an art of the watercloset," the only place where a soldier could express himself.

I do believe that it is not so much an anatomic organ inferiority in question, but an inferiority of organ function that matters, and that the seeds of "colitis" are probably sown by the strict mother who trains her small child to habits of cleanliness with too much severity, impressing on the child how inferior it is not to be able to regulate its bowel function better.

It is remarkable how so often in these cases the dominant mother has cropped up—particularly the widow, who in the absence of the father has a reinforced authority. On the part of the patient there seems to be a remarkably childish outlook, a submission to the wishes of her parents, a lack of initiative in tackling the problem of earning a living; notice how many of the patients disliked their occupations, and were relieved to escape them by colitis. Of the young unmarried patients, 2 had no interest in the opposite sex, the third had become engaged to a man she must have known the rest of the family would disapprove of.

I have described no men in my series, but Murray had 7 reports in this paper of men who were all tied to their mothers. Though they "felt cramped," they hadn't got the guts to look for a mate.

This was the situation of my older patient, who rather than forge out a career had contented herself with a life of humiliating subservience as a dependent on a mother substitute.

I believe that "colitis" is often the somatic expression of the emotional conflict between the reality, "You must grow up," and the phantasy, "I want to retain my childish dependence on my mother."

The beginning of "colitis" is a "psychogenic mucorrhea,"[14] determined by an "overdependence on the parental love and shelter"[15] and often aggravated by the death of the father.

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THE COMMON DENOMINATOR OF DISEASE.*

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The common denominator of all human diseases is a variant represented by the individual person within the patient. The factor which is generally designated "etiologic agent," also a variable, might then be viewed as the numerator. From this standpoint there can be no doubt that physicochemical energy represented, for example, by the activity of the meningococcus alone is not meningitis, nor is the effect of the metal lead *per se* equivalent to anemia and colic. The principle, likewise, holds for energy expressed in terms of emotion which, at present, is classed in the world of imponderables. Consequently, it may fairly be said that the result of

* Presented at the meeting of the Association of American Physicians at Atlantic City, May 7, 1935.

fear alone is neither hyperthyroidism nor peptic ulcer. As a corollary to this proposition, one may state that the coördinates, meningococcus, lead and fear, are not the cause but rather part causes, respectively, of meningitis, plumbism and peptic ulcer. For the incidence, intensity and variation in the clinical picture of these three pathologic reactions is determined in large, yet ever-changing, measure by the other necessary factor, namely, the essential quality of the affected individual.

If we accept this ancient thesis, then, as physicians we are obligated to inquire into the nature of the man as precisely as we now do into the destructive agents which beset him. In the past this was done by the best clinicians in purely empirical fashion. The great doctors of earlier days had an uncanny "feeling" for the man within the patient, an intuitive perception of his special nature. But this sixth medical sense has been well nigh impossible to transmit to students, nor could it be crystallized in any sort of valid formula. Consequently, coincident with the effort in recent years to establish truth by mathematics, it has been to some extent neglected.

Now there are two important questions which at present confront clinical medicine, namely: Whether or not the doctor's understanding of the human animal as a total living organism is adequate; and whether or not this knowledge, so necessary to the clinician, can be moved from the sphere of empiricism to that of science.

At the Constitution Clinic in the Presbyterian Hospital we have approached these questions from the point of view which organismal biologists entertain toward any living creature, be it ameba, sea anemone or the larvæ of amblystoma. The work of the earlier medical natural historians, Hippocrates,[1] Aristotle,[2] Linnæus,[3] and that of the later group, Jacques Loeb,[4] Ritter,[5] Conklin,[6] Morgan,[7] Vogt,[8] Spemann,[9] Coghill,[10] and Cannon,[11] has pointed the way. (1) They have queried, What is the creature's appearance, and (2) How does it behave?

But to be a student simply of the person within the patient is always a difficult task for the physicians and sometimes an impossible one. When an acutely ill man appeals for relief, swift examination of the nature of the malady and prompt treatment is the first obligation. Furthermore, the symptoms and signs of the pathological process strike so forcibly upon the senses that they obscure the individual behind them. It is likewise in general true, except perhaps in the sphere of infection, that as somatic change waxes with chronicity, tests by physical and chemical methods become increasingly spectacular. Such hazards to direct observation of the person which lie in the clinician's path, however, do not exist, as MacKenzie[12] pointed out, to the same degree when the sick man is seen at the very start of his malady. At such a time the so-called "ravages of disease" have not yet distorted the appear-

ance and conduct of the human organism's "total personality." The physician may still view him as an organismal entity. Yet even the destructive influence of prolonged illness never quite obliterates the strange quality or flavor of the man within the patient. This personal specificity is highly durable and to the end stubbornly resists destruction. It is illustrated, for example, by the discovery that grafted tissues never lose their specificity; or by Wheeler's[13] observation, that ants, enclosed in amber from an epoch 2,000,000 years in the past can be identified with forms which crawl today.

The principle also appears in history in the persistence of the Hapsburg lip and the Bach family's musical gift. In the clinic or general practice, physicians are familiar with the persistence of the original personality. One has only to remind the reader of the tall slender youth, with dark coloring and silent aloof demeanor who does not mix well with his fellows at school. Some years later the shadow of that boy may be glimpsed in the sullen paranoid or rigid close-bent catatonic schizophrenic.

In the sphere of so-called bodily disease a similar picture might be drawn of the large, deep-chested, heavy youth, with very broad, short face, whose blue eyes are set far apart and whose pink cheeks and exceptionally fine, silky hair are the joy and pride of his mother. Yet his rather neutral, gentle, fireless disposition somewhat disappoints her. Many years later, she or the old family doctor sees the shadow of that florid youth beneath the light, tawny skin, soft, flaccid tissues, and pale, lusterless blue eyes of the patient with pernicious anemia.

And so it would seem that as change proceeds in somatic tissues, both functional and structural, modification of the animal's original character ensues. Yet no matter how greatly this individuality be distorted by advancing disease, its essential quality is never obliterated. It seems to be the most tenacious quality of living creatures, imperishable in the individual so long as the race survives, yet far less well explained than are many of the detailed processes which, acting together, subserve the biologic purpose of the living organism. In commenting on these matters, Jacques Loeb writes: "The definiteness and constancy of each species must be determined by something equally definite and constant in the egg, since in the latter the species is already fixed irrevocably."

Yet while this species constancy is fixed in the egg, the organism reacts quite differently to external stimuli at different stages of the growth and development. These differences seem to depend upon the successive addition of parts which are necessary to the finished whole. Thus Murphy[14] showed that foreign tissue was accepted by and would grow in the chick embryo before the twenty-first day, when spleen and lymphatic tissue appeared. After that stage, evidently related to some change in the whole embryo produced

background, except that life in the institution had been pretty grim. As the "colitis" persisted after admission, I think the possibility of the self-administration of abortifacients can be excluded.

I have another case of "colitis" in pregnancy in my hospital file:

CASE 9.—A married woman, aged 23, a small, fluffy blonde, whom newspaper reporters could hardly avoid describing as a girl bride. She was the youngest of 7 children. Her father died when she was 13. Another widowed mother. Her mother, she remembered, use to dose her with syrup of figs as a child. On leaving school she became a maid at a boarding house and married the visiting milkman at 19. They lived at first in rooms near her mother, but 2 years later the milkman bettered himself and installed his wife in a brand new Council house in a garden suburb some miles away from his mother-in-law. Within a few months of the separation my patient developed pain, sickness and diarrhea. This illness invalided her for 9 months, and had the much desired result of bringing her mother to the rescue, ostensibly to do the housekeeping. She recovered, and all went smoothly for 9 months. Then a relapse set in. She was admitted to my ward 2 months later, and I found on examination that she was 3 months pregnant. I also discovered that she had not told her husband or her mother of the amenorrhea; further, that she was scared stiff about the pregnancy, having heard some realistic descriptions of labor from her young married acquaintance. She began to improve after reassurance, but unfortunately I dieted her rather strictly, as vegetables and fruit increased the secretion of mucus. She developed a pellagra-like condition, with pigmentation, pustular rash, stomatitis and paresthesias. Wallwork, in a discussion at the Cabot Clinic, described a similar sequel during the treatment of a case of ulcerative colitis. She could not tolerate bemax or marmite, and before I could give her more than one dose of liver as a source of vitamin B she aborted. After the miscarriage she rapidly improved.

And now I want to describe another type of case which I think of as the "rolling stone." More accurately, I am thinking of the middle-aged spinster who has never been trained to earn her living, and who, as Barber said of a case of mucous colitis, "remained at home a failure."

CASE 10.—One example I dealt with recently was a lady, aged 57. Since the age of 17 she had always been subject to "attacks" of diarrhea when she was preparing for any special occasion. She started work as a milliner. She had to take it up, she said, but she loathed it, and at the end of 5 years she developed "colitis" and retired from the commercial struggle. Eight years later she was still hoping for a cure, and underwent a curettage, believing she would get some relief. Two years later she was admitted to a London hospital for observation and was discharged with the information that her case was incurable. Having no means of her own, and 4 brothers, all married with young families to support, she attached herself to a wealthy but delicate cousin as a companion, and for 20 years she maintained a roof over her head by adapting herself to the whims of a semi-invalid. This tyrannical old lady did not permit her companion to leave her even when her mother was seriously ill, but graciously extended her a day's leave to go up for the funeral.

Even this bereavement did not provoke a diarrhea, but 9 months later the rich employer had to enter a nursing home for a serious operation. The prognosis of the surgeon was very grave, and so my patient was at last brought face to face with the precarious reality of her existence and

suddenly collapsed with sickness and
phobia was that the other patients in the ward were going to die, an obvious projection of her terror that her protector was about to perish. She told me that she felt abandoned, that she had no claim on anybody. She made little improvement until the news came that her cousin had survived the operation, had sold her house, and was going to live abroad, and her services, such as they were, would no longer be needed. Her last hope gone, my patient found that when the worst came to the worst, she could face it, and 2 days later she discharged herself, much improved and ready to tackle the world.

CASE 11.—Another patient, aged 66, was the middle child in a family of 5. Always delicate, she never ran about like other children, and was allowed special delicacies on account of her weak stomach. At the age of 17 she developed "colitis" while she was waiting for admission for an operation for strabismus, and passed blood and mucus. She was trained for book-keeping, but she did not like it, and at the end of 5 years gave it up on the pretext that she had to prepare for her marriage which took place a year later. After being married for 20 years her husband left her. Her younger daughter departed to keep house for her father, her elder daughter was married by this time and living in Singapore. Once more she was alone in the great big world; and so she settled down for the next 16 years to a life in London bed-sitting-room, doing unskilled nursing. She gave up this hand-to-mouth existence 4 years ago to come to Bristol to nurse a dying sister. The sister died after 9 weeks and for the next 4 years the patient continued to bolt in and out of boarding houses and convalescent homes wangled from her panel doctors. Having left the metropolitan scene of her labors, she lost her connection, and there was no demand for her services as unskilled nurse in a strange city, and finally when she was sent to me, she had come to the end of her money and resources. She had stayed with all her friends, been to 3 convalescent homes in as many months, and now the "colitis" had begun again. On admission she was Roentgen rayed; the barium meal reached the cecum in good time, but did not progress further than the ascending colon for 48 hours and reached the transverse colon in 96. There was no ptosis but a little diverticulitis. She subsequently survived 10 days without an action of the bowels, without rise of temperature or discomfort. With a technique borne of years of practice she mobilized the good will of the almoner and on discharge had found herself yet another temporary perch.

My last case is another example of the widowed mother-daughter situation:

CASE 12.—The patient was the youngest of a family of 3 girls. The father had died when she was young. This girl was the brains of the family, who saw to it that these were duly exploited. As a librarian, she kept the rest of the family, and was expected, after long hours, to come home and do the greater part of the housework. The mother was perfectly healthy, but the most selfish woman I have ever heard of. I learned nothing of this from the patient, but from her doctor. For 10 years she was the family Cinderella. Then she developed appendicitis, and was operated upon for a perforated appendix. Once the treadmill of service ceased to revolve, it was difficult to start again. The patient made a slow recovery, keeping to her bed for 5 months. She was never able to resume her work, but stayed at home to listen to the interminable regrets of her mother for the days when the family were better off on her salary. The family, anxious to conserve the source of the golden eggs, sent her to this doctor and that in a hope of getting her back to work again, and eventually an enthusiastic surgeon discovered an alleged septic focus in her tonsils and these were

removed. But their hopes were dashed; she developed "colitis." Roentgen rays showed ulceration of the colon; the stools a non-lactose fermenter, and in 8 months she slowly slipped down hill, in spite of blood transfusions, and died. Her mother characteristically kept away from her deathbed, as she found these scenes so "trying."

I have tried to convey to you this short series of cases the psychologic background of "colitis," as I have seen it. The President[10] has already described a case in his paper and C. D. Murray,[11] in America, has also published a short article on this question.

I think we can claim that many of these cases begin as an alteration in function of the vegetative nervous system, which selects the colon as the battlefield on which the emotional conflict is fought out. As 1 patient of Bockus[12] said: "The amount of mucus in my bowel is a barometer of my nervous state." I have never been able to satisfy myself in my own cases that there was any organ inferiority in bowels. Many of my patients had a normal bowel without ptosis or kinks, or redundant folds.

Perhaps it is as Larionov,[13] the Russian artist, said of some paintings produced by artists when serving their term of conscription in the army, "an art of the watercloset," the only place where a soldier could express himself.

I do believe that it is not so much an anatomic organ inferiority in question, but an inferiority of organ function that matters, and that the seeds of "colitis" are probably sown by the strict mother who trains her small child to habits of cleanliness with too much severity, impressing on the child how inferior it is not to be able to regulate its bowel function better.

It is remarkable how so often in these cases the dominant mother has cropped up—particularly the widow, who in the absence of the father has a reinforced authority. On the part of the patient there seems to be a remarkably childish outlook, a submission to the wishes of her parents, a lack of initiative in tackling the problem of earning a living; notice how many of the patients disliked their occupations, and were relieved to escape them by colitis. Of the young unmarried patients, 2 had no interest in the opposite sex, the third had become engaged to a man she must have known the rest of the family would disapprove of.

I have described no men in my series, but Murray had 7 reports in this paper of men who were all tied to their mothers. Though they "felt cramped," they hadn't got the guts to look for a mate.

This was the situation of my older patient, who rather than forge out a career had contented herself with a life of humiliating subservience as a dependent on a mother substitute.

I believe that "colitis" is often the somatic expression of the emotional conflict between the reality, "You must grow up," and the phantasy, "I want to retain my childish dependence on my mother."

The beginning of "colitis" is a "psychogenic mucorrhea,"[14] determined by an "overdependence on the parental love and shelter"[15] and often aggravated by the death of the father.

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THE COMMON DENOMINATOR OF DISEASE.*

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The common denominator of all human diseases is a variant represented by the individual person within the patient. The factor which is generally designated "etiologic agent," also a variable, might then be viewed as the numerator. From this standpoint there can be no doubt that physicochemical energy represented, for example, by the activity of the meningococcus alone is not meningitis, nor is the effect of the metal lead *per se* equivalent to anemia and colic. The principle, likewise, holds for energy expressed in terms of emotion which, at present, is classed in the world of imponderables. Consequently, it may fairly be said that the result of

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fear alone is neither hyperthyroidism nor peptic ulcer. As a corollary to this proposition, one may state that the coördinates, meningococcus, lead and fear, are not the cause but rather part causes, respectively, of meningitis, plumbism and peptic ulcer. For the incidence, intensity and variation in the clinical picture of these three pathologic reactions is determined in large, yet ever-changing, measure by the other necessary factor, namely, the essential quality of the affected individual.

If we accept this ancient thesis, then, as physicians we are obligated to inquire into the nature of the man as precisely as we now do into the destructive agents which beset him. In the past this was done by the best clinicians in purely empirical fashion. The great doctors of earlier days had an uncanny "feeling" for the man within the patient, an intuitive perception of his special nature. But this sixth medical sense has been well nigh impossible to transmit to students, nor could it be crystallized in any sort of valid formula. Consequently, coincident with the effort in recent years to establish truth by mathematics, it has been to some extent neglected.

Now there are two important questions which at present confront clinical medicine, namely: Whether or not the doctor's understanding of the human animal as a total living organism is adequate; and whether or not this knowledge, so necessary to the clinician, can be moved from the sphere of empiricism to that of science.

At the Constitution Clinic in the Presbyterian Hospital we have approached these questions from the point of view which organismal biologists entertain toward any living creature, be it ameba, sea anemone or the larvæ of amblystoma. The work of the earlier medical natural historians, Hippocrates,[1] Aristotle,[2] Linnæus,[3] and that of the later group, Jacques Loeb,[4] Ritter,[5] Conklin,[6] Morgan,[7] Vogt,[8] Spemann,[9] Coghill,[10] and Cannon,[11] has pointed the way. (1) They have queried, What is the creature's appearance, and (2) How does it behave?

But to be a student simply of the person within the patient is always a difficult task for the physicians and sometimes an impossible one. When an acutely ill man appeals for relief, swift examination of the nature of the malady and prompt treatment is the first obligation. Furthermore, the symptoms and signs of the pathological process strike so forcibly upon the senses that they obscure the individual behind them. It is likewise in general true, except perhaps in the sphere of infection, that as somatic change waxes with chronicity, tests by physical and chemical methods become increasingly spectacular. Such hazards to direct observation of the person which lie in the clinician's path, however, do not exist, as MacKenzie[12] pointed out, to the same degree when the sick man is seen at the very start of his malady. At such a time the so-called "ravages of disease" have not yet distorted the appear-

ance and conduct of the human organism's "total personality." The physician may still view him as an organismal entity. Yet even the destructive influence of prolonged illness never quite obliterates the strange quality or flavor of the man within the patient. This personal specificity is highly durable and to the end stubbornly resists destruction. It is illustrated, for example, by the discovery that grafted tissues never lose their specificity; or by Wheeler's[13] observation, that ants, enclosed in amber from an epoch 2,000,000 years in the past can be identified with forms which crawl today.

The principle also appears in history in the persistence of the Hapsburg lip and the Bach family's musical gift. In the clinic or general practice, physicians are familiar with the persistence of the original personality. One has only to remind the reader of the tall slender youth, with dark coloring and silent aloof demeanor who does not mix well with his fellows at school. Some years later the shadow of that boy may be glimpsed in the sullen paranoid or rigid close-bent catatonic schizophrenic.

In the sphere of so-called bodily disease a similar picture might be drawn of the large, deep-chested, heavy youth, with very broad, short face, whose blue eyes are set far apart and whose pink cheeks and exceptionally fine, silky hair are the joy and pride of his mother. Yet his rather neutral, gentle, fireless disposition somewhat disappoints her. Many years later, she or the old family doctor sees the shadow of that florid youth beneath the light, tawny skin, soft, flaccid tissues, and pale, lusterless blue eyes of the patient with pernicious anemia.

And so it would seem that as change proceeds in somatic tissues, both functional and structural, modification of the animal's original character ensues. Yet no matter how greatly this individuality be distorted by advancing disease, its essential quality is never obliterated. It seems to be the most tenacious quality of living creatures, imperishable in the individual so long as the race survives, yet far less well explained than are many of the detailed processes which, acting together, subserve the biologic purpose of the living organism. In commenting on these matters, Jacques Loeb writes: "The definiteness and constancy of each species must be determined by something equally definite and constant in the egg, since in the latter the species is already fixed irrevocably."

Yet while this species constancy is fixed in the egg, the organism reacts quite differently to external stimuli at different stages of the growth and development. These differences seem to depend upon the successive addition of parts which are necessary to the finished whole. Thus Murphy[14] showed that foreign tissue was accepted by and would grow in the chick embryo before the twenty-first day, when spleen and lymphatic tissue appeared. After that stage, evidently related to some change in the whole embryo produced

with the addition of lymphatic substance, foreign tissue was rejected. The observations of Stockard[15] on trout embryo showed that the different viscera appeared at definite times in the developmental process, each new budding organ holding what he called a "moment of supremacy." But though it would seem from these experiments that the parts were in a sense directive of the whole, the more recent studies of Coghill[10] upon amblystoma embryos indicate the reverse. "In like manner," he writes, "the tissues of the tongue receive branches from motor neurones that are engaged in integrating the trunk long before the tongue has muscle tissue in it. It is, therefore, the potentiality of the functional neurone to grow in embryonic fashion that gives to the organism as a whole its ability to subjugate new parts and thereby maintain its unity during the development of behavior. Such growth of the already conduction neurones accomplishes, then, the primary function of the nervous system: the maintenance of the integrity of the individual while the behavior pattern expands."

This statement expresses well the notion that whatever may be the purpose behind the "definiteness and constancy of each species," at least it results in the fact that all the processes in the growing and developing embryo and young animal move toward the eventual production of a finished whole—a complete organism to which each part is subservient. For the clinician the organismal concept may be more significant than is at present generally accepted. There has been so much detailed information about individual organs obtained during the past decade by highly specialized methods that these have naturally become the focal points of medical interest. As I have recently stated: "The difficulty, however, with this sort of knowledge of human beings is that the skeleton, the muscles, or the organs are only those and quite useless until each and all combine and function smoothly together in the service of some particular person."[16]

The student of human constitution, or clinical organismalism, would have an easier task if man's reactions to environment were, like those of an ameba or earthworm, limited to physical nature. So far as we know, the life conduct of those forms expresses simple reflex response to direct physical and chemical stimuli. Consequently, the interaction between the living organism and its special environment at that level is less difficult to observe and interpret than is so in man. In his case the creature himself is infinitely complicated and dwells, furthermore, at one and the same time in two separate and complete worlds, those of reality and phantasy. Indeed, it is often impossible to determine which one supplies the adverse stimulus, or "external agent" of his illness. It becomes necessary, therefore, to investigate the zone wherein the human organism's envelope, physical and psychologic, merges with its special environment. Such inquiries should properly cover every

stage of the individual's growth and development and include each detail of conscious memory and as much of the hidden content of the subconscious as can be retrieved by adequate psychologic technique. Thus it is apparent that the study of the man within the patient actually becomes the study of the "man-environment unit." Fig. 1 presents the idea in diagrammatic form.

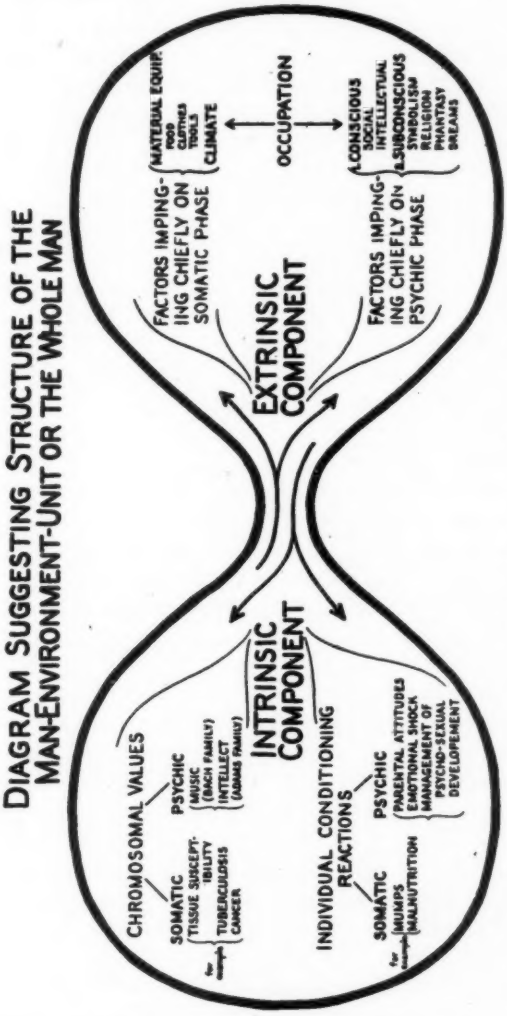

FIG. 1.—Note the arrows representing the flux of interacting forces which form the continuity between living organisms and their individual environments. (From New York State J. Med., 34, 11, 1934.)

The main problem, however, which confronts the clinical organismalist, or student of human constitution in relation to disease, is to be able to evaluate correctly the man or woman whose disease he is called upon to cure. For the moment let us fix our attention upon the man himself as a specific part cause of his own malady.

Like every living organism there are two phases of his being to be considered. The first of these is his form and size, which are the end results of growth and development. These in turn rest upon inherited and conditioning influences. The bones, joints and skeletal muscles combine to enable the animal to negotiate successfully, under the direction of the psychophysiologic command, such time-space relationships as are necessary to its wellbeing. Second, we have to investigate that far more complex and obscure combination of viscera which control the inner life of existence and procreation. The main elements in this extraordinary phase of the human being can be designated as cortex, thalamus and hypothalamus, autonomic nervous system, endocrine glands and smooth muscles. This complicated system will hereafter be referred to as the corticothalamus mechanism. These are the physical, structural units, but there is still another factor which is difficult to place, yet which seems to direct the whole—namely, emotion. The scope and purpose of this communication, however, does not permit full discussion of the psychology of emotion. But because the matter is one of such great significance in the problems of internal medicine, and especially because the quality and intensity of emotion and its effects upon physiologic processes is so specific and variable among human beings, it is necessary to deal with it as an essential element of the total organism.

For a good many years the theories of emotion advanced by James and Lange[17] were accepted as final. They were so nearly alike that their tenets have usually been spoken of together, as the James-Lange theory. As Cannon states briefly: "These observers believed that the chief point of the felt emotion depended on the visceral and organic part of the expression." But with new methods to assist him, together with supporting observations from the surgical findings of Cushing,[18] W. B. Cannon reached a much more satisfactory idea of the nature and source of emotion.

Fig. 2 shows in diagrammatic form Cannon's thalamic theory of emotion, with the addition of a plan to link the mechanism of repressed or forgotten memories and symbolic stimuli to the whole. This supplement seemed to be desirable from the clinical standpoint for there can no longer be doubt that the emotional patterns, buried deep in the subconscious mind, are capable of producing changes in physiologic function. Indeed, even before Freud, there were many indications in the literature from earliest folklore to the writings of Schopenhauer and of Nietzsche that men recognized this fact. And so it seems probable that by lifting the thalamus into the surprising position it now holds in the apparatus of emotion, Cannon has gone far to unite the work of internist and psychiatrist.

If we now turn to the problem of applying the organismal point of view to the clinic we are immediately faced, as in all other scientific research, with the question of methods. In general, these fall

into two classes: (1) Those which are applicable to the body structure, or architecture; (2) those which relate to organic function and conduct of the individual as a whole. Direct observation by

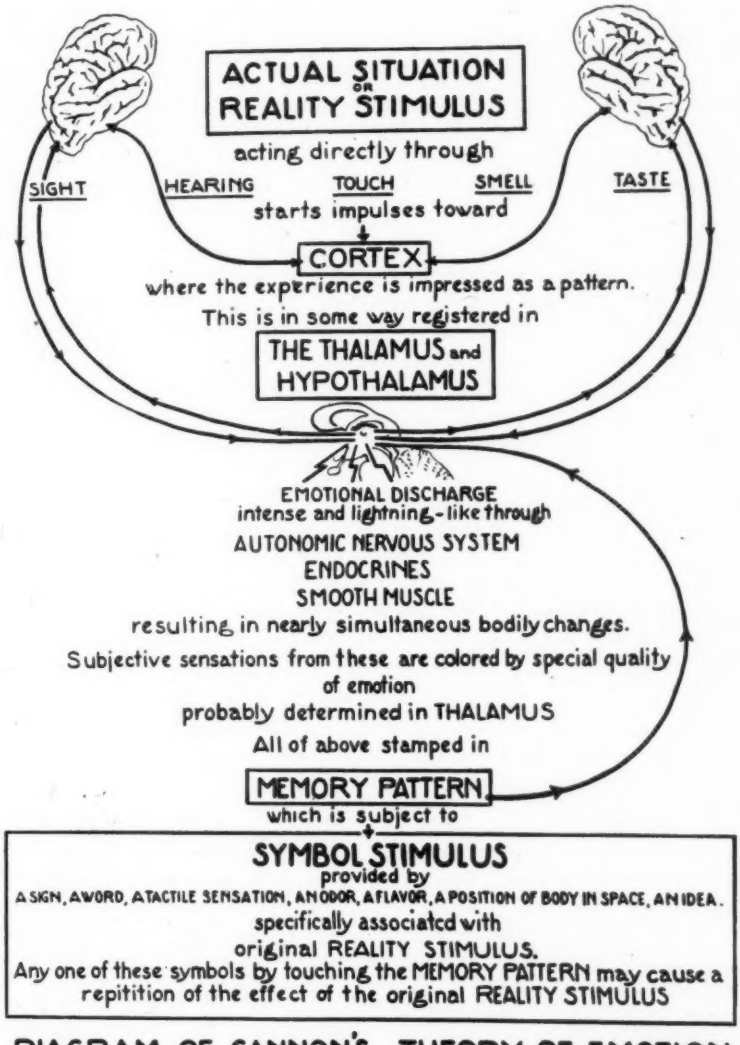
ACTUAL SITUATION OR REALITY STIMULUS
acting directly through
SIGHT
HEARING
TOUCH
SMELL
TASTE
starts impulses toward
CORTEX
where the experience is impressed as a pattern.
This is in some way registered in
THE THALAMUS and HYPOTHALAMUS
EMOTIONAL DISCHARGE
intense and lightning-like through
AUTONOMIC NERVOUS SYSTEM
ENDOCRINES
SMOOTH MUSCLE
resulting in nearly simultaneous bodily changes.
Subjective sensations from these are colored by special quality of emotion
probably determined in THALAMUS
All of above stamped in
MEMORY PATTERN
which is subject to
SYMBOL STIMULUS
provided by
A SIGN, A WORD, A TACTILE SENSATION, AN ODOR, A FLAVOR, A POSITION OF BODY IN SPACE, AN IDEA.
specifically associated with
original REALITY STIMULUS.
Any one of these symbols by touching the MEMORY PATTERN may cause a repitition of the effect of the original REALITY STIMULUS
DIAGRAM OF CANNON'S THEORY OF EMOTION

FIG. 2.—Diagram of Cannon's theory of emotion with addition of memory mechanism and symbol stimulus.

inspection is still perhaps the most valuable means of studying the morphology. Anthropometry, which we have used greatly in the past, probably does not contribute as much as one would demand

from a precise method. It is helpful but does not supply as much information as can be gained from the non-measurable characteristics. The contours formed by soft tissues (muscle and fat), the shape and position of eyes; form, position and quality of teeth; texture and color of skin and hair and the latter's distribution; pigmentation and hyperextensibility of joints; and, finally, the design and size of external genitalia; all these are not measurable characters, yet they usually tell far more about the individual than do measurements. They are the characters which are so grossly modified in the fully developed stages of many well-known endocrinopathies and have been successfully used as aids in endocrinologic diagnosis. Indeed, the slight differences in form, tissue quality, fat distribution, color, which stamp individuality upon a man, may properly be referred to a well-recognized endocrinopathy as to a yardstick.

The first 2 cases to be presented illustrate two phases of the morphology problem. In 1 example the presenting malady is perhaps chiefly foreordained through some genetic fault in the germ plasm. At least no external exciting part cause can be discovered. In the second, the final pathologic situation results in part from the conditioning effects of an infection during the growth period of the organism. But the organism exhibited the developmental fault of cryptorchidism.

CASE 1.—G. H., a cabinetmaker, male, aged 48, complained of weakness, depression, dyspnea on exertion, malaise, numbness of fingers for past 2 years and some pain and heaviness in frontal region. He tells his story in a very soft, gentle, though low-pitched, voice. His expression is not animated and suggests the unemotional, resigned acceptance of life so often seen in gentle, elderly women. This look is rendered more poignant by the delicate wax-colored skin, which is profusely crinkled by very fine lines, like crushed tissue paper. There is scant and spottily distributed hair on the face, which the patient states he has never needed to shave more than twice a week. The teeth are unusually small and there is a wide separation between the central incisors.

Heavy shoulders and a deep, short chest give a first impression of virility, which is supported by apparently large external genitalia. But the rounded contours of the shoulders, trunk, abdomen and hips throw the emphasis more toward a feminine form. Furthermore, though the scrotum is long and rather redundant, the testicles are not large and they can be easily caused to disappear entirely in the inguinal canal. When it is pushed well up, the right testis will remain concealed indefinitely until pushed down again.

The morphologic picture was one which could be compared with the eunuchoid yardstick and represented what may perhaps be called the neuter, or species, type. Further evidence of the reduced virility was the almost complete absence of hair from trunk and extremities. The pubic mass was sharply circumscribed. But the patient's hands struck sharply across the otherwise eunuchoidal conformation. They were very large, thick-set and stubby, with large flat nails. The hands alone could be compared with the yardstick of acromegaly. But this was again belied by the delicate modelling of nose and chin. Only the separated incisors agreed.

In the functional sphere this patient showed, as Cushing pointed out in

1912, that "In many of the cases in which hypopituitarism is the striking feature, traces at least of an early tendency to hyperpituitarism can be detected." This man in early manhood was exceptionally powerful and excelled his fellows in feats of strength (see Cushing,[18] Case 1). In the psychosexual field, likewise, this patient's history revealed a double fluctuation. Thus in his earlier years his libido was laggard, for 2 years after marriage it became exceedingly active, then waned slowly, until 18 months ago, when it disappeared entirely.

On the basis of the total personality, some maladjustment between pituitary and gonad was suspected, and because of the hand conformation and the teeth, attention was chiefly drawn to the pituitary. A radiograph of the skull revealed a large tumor which had nearly destroyed the posterior portion of the sella. There were no neighborhood symptoms.

The detailed description of the personality has not been given to demonstrate the effect on symptoms and signs of the tumor's presence, but rather to promote the notion that the man's constitution is a coördinate of the tumor. This total organism was destined to be unsuccessful. From the start the forces which determined its somatic and psychic characters invited the tumor; they did not result from it. The tumor in that sense inevitably becomes part of an originally faulty whole. One might almost say, "The man is in part the tumor," instead of the customary, "this man has a tumor."

CASE 2.—This patient (reported previously as Case 3, p. 123, *Disease and the Man*, 1930) falls in a category somewhat similar to the first. From the organismal standpoint there were two significant aspects of this man's total personality: (1) As a member of a large clan which showed a strong factor for shortness, he became an outstanding variant in the matter of length growth. (2) The quality of his personality and whole life adjustment were profoundly modified from the expected family pattern by the developmental fault—unilateral cryptorchidism—on the one hand, and the special conditioning accident of unilateral castration by mumps on the other.

The preceding 2 cases were presented to illustrate the importance to clinical medicine of direct observation of the structural plan of a given human being. The following case is offered in demonstration of the difficulties and possibilities of approach to the functional plan of a given individual. It is in this sphere that synthesis of existing knowledge of autonomic nervous system, endocrinology, Cannon's thalamic theory of emotion and psychoanalysis are of first importance.

CASE 3.—An American of Scotch origin, aged 36, a professor, married and has 2 children, girl and boy. He is 6 feet tall, slender, well coördinated and moves with swift easy stride and gesture. His hair is tawny, the skin white, delicate and freckled. His vivid blue-green eyes convey the notes of curiosity, comprehension, fear, cruelty and merriment.

The zygomatic facial zone is broad, interpupillary space 64 mm. (above average of 60 to 61); the cheek zone tapers sharply to a pointed chin. The nose is narrow and acute. The thin compressed lips form a mouth line which is straight and severe. Thus the face is a clear portent of the pattern of his psychic panel: high intellect, unyielding determination, extraordinary sensitiveness, fine feeling and subtle humor. The pace and tension of the entire organism is extreme.

Routine physical examination at the first visit, 7 years ago, disclosed no pathologic structural changes. The heart rate, surprisingly for so tense a person, was 66 even under examination. The blood pressure was 120/80.

There are 3 major symptom phases in his patient's recent medical history. They involve 3 so-called main systems of the total organism—digestive, circulatory, ideational. Since March, 1927, when he first sought relief, the emphasis upon symptoms in each system has had a certain chronologic sequence. But in the entire life story, from the first there appear evidences of disturbance now in 1, now in another of the 3.

1. *Digestive Phase.* At the first visit, in March, 1927, the patient told of 3 similar attacks of terrific abdominal pain, which doubled him up—lasted 12 to 30 hours and left him completely prostrated. As the pain abated he would fall asleep, then awaken suddenly feeling weak and ravenously hungry. A curious and, as it later turned out, most important feature of the hunger was a specific craving for baked beans.

The 4 diagnoses which had been made were: gall stones, perforated peptic ulcer, acute pancreatitis and kidney stone. Physicians who examined him during the attack found no point of especial tenderness but a board-like abdominal wall. In 1 instance preparations for immediate laparotomy were made. The patient objected and instead was given morphin.

Careful questioning revealed that in one instance, for some reason quite unknown to his conscious thinking, he had eagerly read in the newspapers every detail of the last illness of the moving-picture actor, Rudolph Valentino. Two to 3 hours after hearing of Valentino's death the severe attack of pain began. Following the lead of this association, the patient remembered that each one of the other attacks had followed upon hearing or reading of a person who had died of appendicitis or acute general peritonitis. This discovery led, in turn, to the memory of his terror on hearing, at the age of 10, how a friend of his father's died in agony of that disease. From that recollection his thought moved rapidly backward in time to his own nearly fatal illness, cholera infantum, at the age of 2½. This experience had often been recounted to him by his mother, who clung tenaciously to each gruesome detail—how he had writhed in pain, how terrifically his bowels had moved, how she had massaged his tiny, shrunken limbs back to life and how, finally, when he was permitted the first solid food she had given him baked beans which he had ravenously devoured.

For brevity's sake, report of the routine medical tests, which were all negative, will be omitted. The behavior of the stomach, however, is of interest. Following a bismuth draught the stomach was observed first at rest as the fluid entered and then under massage. When this mechanically provoked peristalsis had subsided and the stomach was again quiescent, I leaned down in the dark and whispered in the patient's ear the words, "Rudolph Valentino died of peritonitis." Almost immediately the stomach could be seen to move and soon was again in violent peristalsis. In conscious response to the whispered sentence he laughed and asked if I were "kidding him." Then about 30 seconds to 1 minute later he said, "My God, Doctor, that bismuth must be disagreeing with me, I've got some cramps coming on." (Note delay of subjective sensation.)

This Roentgen ray experience aroused the patient's interest in the emotional origin of his abdominal attacks, and during the next few months he brought in reports of other early memories of digestive upsets, especially of sudden unexplained diarrhea and his mother's great solicitude about them. It appeared that much of his childhood memory centered about her continual concern whether his bowels were moving too little or too much. It should be mentioned at this point that when the patient was 5 years of age his father had died following an operation for gastric ulcer. This experience terrified him, but not so much, he said, as the one when at the age of 3 his father, a great, powerful, bearded man, had carried him on his shoulder into the ocean surf. The waves had broken over him and he felt the pangs of suffocation.

During the next 4 months there were about 20 conferences in which disclosures, germane to the other 2 system disturbances were made. The patient, who is a professor, noticed an increasing difficulty in meeting his classes, feared their criticism and was embarrassed to the point of physical distress, trembling, sweating, palpitation, nausea, weakness and diarrhea.

In discussing the symptom of palpitation it came out that about 7 years before the patient had consulted a doctor in the West who was a large man with a very deep loud voice. During the interview the doctor "looked at me as though I were a convict and asked me if I ever had pains in my stomach. Then he took my blood pressure and said 'My God man, it's 190. Go home—don't walk—take a taxi—and go to bed at once.' I was terrified."

At the close of the 4 months of conferences the patient went away and was not heard from again for 5 years. When he reappeared he complained of attacks of weakness, referred to his heart.

2. *Circulatory Phase.* On November 30, 1932, he reported having been very well, entirely free from abdominal cramps and had held his weight. Now he complains of elevation of blood pressure and fear of stroke. He has been refused standard premium rates by life insurance companies on account of his continued increased arterial tension. His mother has high blood pressure and lately 2 of his friends have suffered strokes.

Examination revealed the blood pressure 160/80 in recumbent position and a very loud pistol-shot sound in the artery. The pressure rose 10 points within a few seconds when I asked for the name of a friend who died of stroke. But on repeated subsequent readings it did not fall below 160. There is sinus arrhythmia and marked slowing on deep held inspiration. The heart is not enlarged. Routine urinalysis and blood chemistry gave normal pictures.

Because he now no longer lived in New York, strict psychoanalytic technique was impracticable. But after 14 months of irregular conferences the blood pressure gradually sank to 130, where it has remained He now pays regular life insurance rates. But as the blood pressure fell, symptoms of anxiety increased.

The first intimation of the ideational phase was suggested by the rather remarkable statement that: "Blood pressure is to me a concept very subtle and powerful like God; like the flashes of lightning and thunder on distant mountains; something way beyond the power of man's volition to cope with; and emphasizes man's inability to do anything about God, who was the ultimate judge on matters of sex and he had decreed that intercourse was sin."

The sense of being overwhelmed, he said, reminded him of being nearly drowned in a swimming tank when he was 10 years of age, when thrown in by a big bully, and also of the time when his father had held him in the breakers at the age of 3, petrified with fear.

3. *Ideational Phase.* At first the phobia was limited to his circulatory system: death from a stroke or heart failure from high blood pressure. These ideas in turn resolved, first, into fear of suicide, and then the more terrifying thought that he might kill his children, his wife, his mother, the doctor, or anyone he met. The mental anguish occasioned by these phobias was almost unendurable. Following each wave of homicidal fear, the patient experienced the sense of collapse and complete disintegration, which he had previously connected with his heart. The symptoms of exhaustion, palpitation, leaky skin and trembling resembled the picture of hyperinsulinism so closely that it seemed desirable to make observations upon the patient's blood-sugar curve before and after a normal meal, but with normal results.

Space does not permit a full account of the psychoanalysis. But there is

ample evidence to show the serious effect upon the patient of the birth trauma, the great sense of inferiority due to his spindle legs and very small genitalia, the strong homosexual trend, arising in the wish to be subjugated by the father, and the fear (or wish) for castration as a solution of the masturbation guilt, and the œdipus situation. Indeed, the fear that masturbation history would be discovered caused this highly intelligent and educated adult to delay 5 years in finally returning to complete his analysis.

Following the resumption of the conferences the analysis went along smoothly and with comparatively little resistance. From this time on he continued to improve, and at present (May, 1935) he is entirely free from abdominal cramps, his blood pressure is normal and the phobias are reduced to occasional slight and transient reverberations. The case shows clearly that because of the same emotional patterns underlying all the symptoms the patient was not cured when the original cramps disappeared 7 years ago, nor when the blood pressure fell to normal last May. He can be regarded as finally cured only when, in addition to the removal of these two system disturbances, the phobias likewise vanish.

These cases have been selected from a large material at the Constitution Clinic for the purpose of illustrating differences between the persons within the patients. The first 2 provide instances of the situation in which the somatic component (somatic in the sense of structure, architecture, morphology) is the more emphatic criterion of the personality. The third displays a form in which the psychic component (psychic in the sense of corticothalamic mechanism, functional, emotional) predominates. The individual quality (constitution) in the former, in general, results from genetic and conditioned faults in growth and development, and contributes to the production of diseases involving those parts of the body which are concerned with the animal's outward or spatial environmental relationships. In this category, for example, are found diseases of bone, joints, skeletal muscles, motor nerves and weight loss or increase. The individual quality (constitution) in the second group in general springs from genetic and conditioned faults in the corticothalamic mechanism and contributes to the production of those diseases involving vital functions supporting the inner life of existence and procreation. Hyperthyroidism, peptic ulcer, Raynaud's disease, asthma and some forms of arterial hypertension may be given as examples of maladies common to the second category. But these two phases or groups must remain very loose ones, for the obvious reason that functionless structure serves no biologic purpose and function cannot be realized without structure.

Now what significance may the foregoing observations hold for therapeutics? It brings us face to face with the question of why or how psychotherapy in some form or other has since time out of mind been one of the most potent agents in the cure of sick people. Clearly, in the first 2 cases with profound structural fault we are at present powerless to do more than to relieve subjective suffering. Probably therapeutic success in the true sense of cure bears an

inverse ratio to the degree and duration of somatic change. But in the last case structural tissue change had not yet advanced to any degree notwithstanding the extreme severity of the symptoms.

I have used Cannon's theory of emotion for the basis of the chart (Fig. 2), and added the lower part about memory patterns to emphasize the importance of symbolism for mankind. It is perhaps not too much to say that if reality situations and memory patterns are capable of causing function-modifying and tissue-changing emotional discharges from the thalamus, appropriate psychotherapy, interpreting and applying individual and racial symbolism effectively may tend reciprocally to remove the destructive patterns by a process of unconditioning. Recently the surgeons have advocated the use of operations which involve removal of portions of the autonomic nervous system or certain endocrines. No doubt there is a point in the advancing process which moves from early functional disturbance to actual tissue change, at which removal of hypertrophied tissue or blocking the channels through which it acts by surgery is the only effective treatment. But we must weigh carefully the relative merits of a therapy which "cures" (*i. e.*, reduces symptoms) by destroying the integrity of the whole and a therapy which by reintegration of the personality restores an adequate balance of the corticothalamic mechanism. But the latter in turn is limited by the quality or constitution of the individual.

Conclusions. 1. The common denominator of human disease is the individual man or woman—the specific total organism—within the patient.

2. The specificity of that organism as part cause of the presenting disease is analogous to the specificity of the exciting agent from environment.

3. The layer at which the organismal envelope and its environment meet is not sharply drawn. The two may be continuous in a physicochemical sense.

4. The fact that man occupies and reacts with two complete universes—reality and phantasy—renders each disease condition doubly complex.

5. The specific quality of individual human organisms is determined largely by the quality and relationships of the 5 structural parts: (1) Cortex, (2) thalamus, (3) endocrine glands, (4) autonomic nervous system, (5) involuntary muscle.

6. Much information about these can be gained by direct observation of form and function of the organism as a whole—amplified by information concerning its various stages of growth and development.

7. Since any living organism is a link in an hereditary stream of special racial and family protoplasm, genetic histories may contribute to the doctor's understanding of the person within the patient.

8. Because man is a complete psychosomatic being, studies of

his psychologic structure are at least of equal importance to internal medicine as are those of the soma. It is possible that what we now term the subconscious is actually composed of memory patterns in the corticothalamus mechanism. This complex carries not only inherited qualities but also phylogenetic and ontogenetic conditioning effects.

9. The studies of internal medicine deal especially with the later purely somatic resultants of the whole disease process and consequently are often concerned with phenomena widely separated from the initial disturbance. This in many instances can be shown (by means of a meticulous history of the person's physical growth and development and of his emotional reactions, both conscious and unconscious) to arise in an early disturbance at the psychophysiologic border. Consequently it is at this point that the sphere of psychiatry (psychoanalysis) relates directly with that of internal medicine.

10. Cannon's theory of emotion and the added memory mechanism indicate how important it is for the physician to search for the specific symbol stimulus. This may require deep psychologic technique, for often the original reality stimulus is lost to conscious recollection.

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BOOK REVIEWS AND NOTICES

CLINICAL TUBERCULOSIS, in two Volumes. Edited by BENJAMIN GOLDBERG, M.D., F.A.C.P., F.A.P.H.A., Associate Professor of Medicine, University of Illinois College of Medicine; Honorary Professor of Medicine, National University of Mexico; formerly Director of the City of Chicago Municipal Tuberculosis Sanitarium. With the Collaboration of 33 Contributors. Pp. 1580; 640 illustrations and 9 color plates. Philadelphia: F. A. Davis Company, 1935. Price, $22.00.

THIRTY-FOUR contributors have produced a very creditable work that presents all the clinical phases of tuberculosis with sufficient completeness and detail to deserve the term "encyclopedic." The text is divided into 13 sections, designated by the letters A to M: unfortunately, each section has its page numbers begin at 1, with the section letter preceding it, a cumbersome and unnecessary procedure. Section A includes chapters on epidemiology, bacteriology, allergic and immunologic considerations, pathology and pathologic physiology of the tuberculous lung. This section is particularly well done. Section B deals with diagnosis, classification of pulmonary tuberculosis, Roentgen-ray findings in adult pulmonary tuberculosis and differential diagnosis. The chapter on physical diagnosis in some respects is rather skimpy. The productions of roentgenograms are only fair and the chapter on Roentgen diagnosis is the only major chapter without references to the literature. Section C and part of Section D, dealing with prognosis and treatment, including the usual hygienic measures and pneumothorax, pneumolysis and oleothorax, conclude Volume I; they are very well done. Volume II takes up surgical apical collapse, thoracoplasty, heliotherapy, tuberculin and climate treatment, tuberculosis in childhood, tuberculous meningitis, miliary tuberculosis, spontaneous pneumothorax, tuberculosis of pleura, intestines, anorectal region, peritoneum, urogenital tract, special sense organs, cardiovascular system, skin, bones and joints, thyroid. There are also chapters on bronchoscopy in the tuberculous, tuberculosis and pregnancy, diabetes, trauma with regard to industrial and compensation considerations, psychopathology. In spite of the numerous contributors there has been surprisingly little duplication and only one omission which the Reviewer discovered: tuberculosis of the adrenals (Addison's disease). The Editor is to be congratulated on his publication. R. K.

THE STORY OF MEDICINE IN THE MIDDLE AGES. By DAVID RIESMAN, M.D. Sc. D., Professor of the History of Medicine and Professor Emeritus of Clinical Medicine, University of Pennsylvania; Member, History of Science Society and Medieval Academy of America. Pp. 402; illustrated. New York: Paul B. Hoeber, Inc., 1935. Price, $5.00.

THE Middle Ages have so long been loosely regarded as the quintessence of intellectual stagnation that it is refreshing to be given two more refutations of this outworn *cliché*. Just as Dr. Riesman's book with its background of general medieval university life and customs makes this amply apparent, so does Morison's "Founding of Harvard College" with its generous treatment of the medieval universities and their activities, without which none of the older American universities can be properly understood. As Dr.

Riesman points out in his Preface "the people who produced the Great Cathedrals, the French Chansons, the German Minnelieder, the Magna Charta, Parliamentary Government and above everything, the Universities (and one might add, Hospitals), deserve our gratitude and admiration." Beginning with the Greek inheritance, the School of Salerno, Arabian Medicine and medieval Jewish physicians, the ever changing medical stream is followed in the first third of the book through clerical and scholastic medicine, astrology and alchemy to the six leading universities of the period —two each in France, Italy and England. Far outgrown as the volume is from its original destination as a unit of the Clio Medica series, yet one cannot but regret that the universities—a most interesting and important phase of medieval life—could not have even more complete treatment. From a second point of view, such subjects are then treated as anatomy, surgery, the guilds, medieval diseases and epidemics, treatment, hospitals, and medical textbooks. Paracelsus alone is distinguished by a chapter to himself. The vexed question of the origin of European syphilis is presented thoroughly and impartially. As was to be expected, a verdict of non-proven had to be given for the views of both Americanists and anti-Americanists. One finishes this really very interesting and instructive volume with satisfaction in the reflection that a busy consultant should have acquired such a store of historical knowledge and have had the ability and given the time and care necessary to present in such an attractive form. E. K.

A Bibliography of the Poem Syphilis Sive Morbus Gallicus, by Girolamo Fracastoro of Verona. By Leona Baumgartner and John F. Fulton. Pp. 157; 9 illustrations. New Haven: Yale University Press, 1935. Price, $5.00.

This bibliography of Fracastoro's justly celebrated poem follows, appropriately, close on the heels of the appearance of the one-hundredth printing of the poem (Am. J. Med. Sci., **189**, 864, 1935). Only the *Regimen Sanitatis* of the School of Salernum, among medical poems, surpasses or even equals this record, though its intrepid bibliographer of our day has, alas, yet to appear.

Following a characteristic introduction by Dr. Arnold Klebs, the present bibliography lists the editions by languages, Latin (42), Italian (29), English (13), French (9), German (5), Spanish and Portuguese (one each). These include the usual appearances in collected works and anthologies, which, in some instances, enjoyed more than a single edition. A number of editions represented by unique or very few copies, and consequently generally unknown, are here brought to attention—one of the more obvious fruits of such a bibliography.

The 68 holding libraries recorded are not indexed as regards the individual sums of their holdings, but it is possible to discover that the owners of the largest number of editions are, first, Dr. Fulton himself, and, second, the British Museum. Among the American public or semi-public libraries, the chief holders appear to be, in order, the three largest medical libraries, those of the Surgeon-General, the New York Academy of Medicine, and the College of Physicians of Philadelphia.

The description of the editions is, however, happily far more than merely statistical. The notes on typography, printers, translators, editors, and owners invite the pleasurable dalliance of bibliophiles generally; and it may be presumed that every peruser of *Antiquariatskatalogen* will henceforth find the work, as indispensable for reference as Keynes' bibliography of Harvey or Dr. Fulton's own bibliography of Robert Boyle. It contains, also, a valuable section devoted to biographical and critical material on Fracastoro and his work.

In its general appearance, the book, involving complicated problems in typography, reflects unusual credit upon the ingenuity and taste of the authors and their printers. The world of scholarship, and particularly that section of it concerned with the history of medicine, owes a great debt to the authors for this humanistic bibliography of one of the brightest ornaments of medical *belles lettres*. W. McD. 2D.

THE WOMAN ASKS THE DOCTOR. By EMIL NOVAK, M.D., F.A.C.S., HONORARY D.SC. (DUBLIN), Associate in Gynecology, Johns Hopkins Medical School; Former Vice-President American Gynecological Society. Pp. 189. Baltimore: The Williams & Wilkins Company, 1935. Price, $1.50.

THOUGH recognizing the latent danger in a little knowledge, the author offers this discussion of those problems in which all women are interested, much as a gynecologist would answer the questions put to him by an intelligent patient. Especially interesting are the opening chapters on "What is Femaleness"—a very modern subject—and "Superstition and Folk-lore of Menstruation." Other topics cover the anatomy and function of female organs at various stages of life, and a few disorders such as dysmenorrhea, sterility, leucorrhea and cancer. One is inclined to agree that the danger of a woman attempting to use knowledge gained by reading such a book as a basis of self-treatment is indeed slight. E. K.

CLINICAL MANAGEMENT OF SYPHILIS. By ALVIN RUSSELL HARNES, M.D., Chief of Congenital Luetic Clinic, New York Hospital. Pp. 71; illustrated. New York: The Macmillan Company, 1935. Price, $1.50.

THIS booklet of less than one hundred pages is an effort to render specific, within a very brief compass and at little expense, the technique of the treatment of syphilis, too often only vaguely grasped in the abstract.

The idea is a laudable one but unfortunately its fulfillment in this work leaves much to be desired. Valuable space is wasted on extraneous and unimportant matters, instructions while apparently detailed frequently lack important points and have a sketchy quality not entirely compensated by the efforts at tabulation. For a work dated 1935 to completely overlook the notable American and international contributions to the technique of early and latent syphilis is a grave omission. Sharp exception could be taken to a number of statements and the thing, at least as rendered in words (see p. 18) is at times almost embarrassingly naive. The illustrations are of course drawn to save expense, but have unfortunately lost all their teaching value in the process.

A second edition of this manual will doubtless be called for and an elimination of diffuse material and closer attention to the established landmarks in the recent literature will greatly increase the value of this very useful work. J. S.

THE DOCTOR'S BILL. By HUGH CABOT. With an Introduction by A. LAWRENCE LOWELL. Pp. 313. New York: Columbia University Press, 1935. Price, $3.00.

THIS volume adds another point of view to the rapidly growing literature on the subject of the economic side of medical practice. Its structure is logical and the discussions are fairly impartial but wholly critical.

The author first presents the contrast of medical education and prac-

tice in the decade or so before the present century and the education and practice of the present time. He strips the old practitioner of much of his romance and glamor but on the other hand seems to overemphasize the importance of the use of laboratory procedures in the practice of today.

Dr. Cabot then proceeds to set forth the fundamental axioms and corollaries necessary to attack the problem of medical economics. And truly this is more complex than any theorem ever conceived by Euclid or his disciples! Chapters on the general practice of medicine, specialists and group practice, health services, workman's compensation, analyses of the incomes of physicians and their public are clearly and succinctly discussed. He then summarizes the situation in Europe, with terse comparisons when necessary to point out differences in public customs and requirements.

In his chapters on "Medical Needs in the United States," "Some Suggested Methods of Improvement," and "Where do we go from Here?" Dr. Cabot critically analyzes our needs according to his own ideas. He freely criticizes the attitude of the American Medical Association in opposing all change except that emanating from Dearborn Street, but offers no panacea and backs no other single plan. However, he seems to align himself with "those practitioners under forty-five years" whom he states are all liberals and who are for changes in the existing order. As one who is really under that age, the Reviewer cannot subscribe to his appraisal. There are still a large number of young physicians who prefer the process of evolution to that of revolution and who only occasionally use the airplane as a means of transportation.

If Dr. Cabot can be said to offer any prophecy, it would be the future development of the group clinic in its several different forms. Perhaps that is because Dr. Cabot has usually been engaged in some form of group practice. On the whole the book is thoroughly readable and is recommended for physician or layman. E. T., Jr.

NEW BOOKS.

Gynecological and Obstetrical Tuberculosis. By Edwin M. Jameson, B.S., M.D., Fellow of Trudeau Foundation; Attending Surgeon, Saranac Lake General and Reception Hospitals. Pp. 256; 31 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $3.50.

The Theory and Practice of Anaesthesia. By M. D. Nosworthy, M.A., M.D., B.Ch. (Cantab.), Anaesthetist to Westminster Hospital and Grosvenor Hospital for Women, etc. With a Foreword by I. W. Magill, M.B., B.Ch. (Belfast), Senior Anaesthetist to Westminster Hospital, etc. Pp. 223; 35 illustrations. London: Hutchinson & Co. Ltd., 1935. Price, 12/6.

Gastritis and Its Consequences. By Knud Faber, M.D., LL.D.E., F.R.C.P.E. Hon., Professor of Internal Medicine in the University of Copenhagen. Pp. 119; 48 illustrations: New York: Oxford University Press, 1935. Price, $3.00.

Die Molekularpathologie der Entzündung. Ihre Bedeutung für das Krankheitsverstehen und Krankheitsheilen. Eine Einführung für Studierende und Ärzte. By Professor Dr. H. Schade, Direktor des Institutes für Physikochemische Medizin an der Universität Kiel. Pp. 100; 20 illustrations and 18 tables. Leipzig: Theodor Steinkopff, 1935. Price, Rm. 5.50.

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Methods and Materials of Health Education. By JESSE FEIRING WILLIAMS, M.D., Teachers College, Columbia University, and FANNIE B. SHAW, M.A., University of Florida. Pp. 331; illustrated. New York: Thomas Nelson & Sons, 1935. Price, $1.65.

Die Störungen des Lichtreflexes der Pupille bei den luetischen Erkrankungen des Zentralnervensystems. Beiträge zur Frühdiagnostik der Lues nervosa. By DR. MED. OTTO LÖWENSTEIN, seither ordentl Professor und Direktor des Pathopsychologischen Instituts der Universität Bonn, etc. Pp. 92; 31 illustrations: Basel: Benno Schwabe & Co., 1935. Price, Fr. 5.

A Bibliography of Two Oxford Physiologists, Richard Lower (1631–1691) and John Mayow (1643–1679). By JOHN F. FULTON, M.A. (OXON.), Sterling Professor of Physiology in the Yale University School of Medicine. Pp. 62; 7 illustrations. (Price not given.)

The Medicine-Man of the American Indian and His Cultural Background. By WILLIAM THOMAS CORLETT, M.D., L.R.C.P., (LOND.), Professor Emeritus of Dermatology-Syphilology, Western Reserve University; Fellow of the Royal Society of Medicine of Great Britain, etc. Pp. 369; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $5.00.

The Doctor and the Public. A Study of the Sociology, Economics, Ethics, and Philosophy of Medicine, Based on Medical History. By JAMES PETER WARBASSE, M.D. Pp. 572; illustrated. New York: Paul B. Hoeber, Inc., 1935. Price, $5.00.

NEW EDITIONS.

Arthritis and Rheumatoid Conditions. Their Nature and Treatment. By RALPH PEMBERTON, M.S., M.D., F.A.C.P., Professor of Medicine in the Graduate School of Medicine, University of Pennsylvania; Physician to the Abington Memorial and Bryn Mawr Hospitals, etc. Pp. 455; 69 illustrations, 60 tables, and a colored plate. Second Edition, thoroughly revised. French translation of First Edition, 1933. Philadelphia: Lea & Febiger, 1935. Price, $5.50.

A Synopsis of Regional Anatomy. By T. B. JOHNSTON, M.B., CH.B., Professor of Anatomy, University of London, Guy's Hospital Medical School. Pp. 460; 11 illustrations. Third Edition. Philadelphia: Lea & Febiger, 1935. Price, $4.50.

The Principles and Practice of Medicine. Designed for the Use of Practitioners and Students of Medicine. Originally written by the late SIR WILLIAM OSLER, BT., M.D., F.R.S., Formerly Fellow of the Royal College of Physicians, London; Regius Professor of Medicine, Oxford, etc. Pp. 1196; 22 illustrations, 16 charts. Twelfth Edition; Revision by THOMAS MCCRAE, M.D., Fellow of the Royal College of Physicians, London; Professor of Medicine, Jefferson Medical College, Philadelphia, etc. New York: D. Appleton-Century Company, Inc., 1935. Price, $8.50.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut.-Colonel, M. R. C., U. S. Army, etc. With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Pp. 1573; 945 illustrations, including 283 portraits. Seventeenth Edition revised and enlarged. Philadelphia: W. B. Saunders Company, 1935. Price, Plain, $7.00; Thumb Index, $7.50.

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THE FEMALE URINARY ORGANS.

Ureteral Injuries. There can be no doubt that the ureter is injured in the performance of pelvic operations in a greater number of instances than the literature would indicate. If the operator realizes that he has injured a ureter he is naturally reticent about discussing it, while in many instances the injury is not recognized at the time that it occurs. In discussing this subject Brown[1] states that the diagnosis of ureteral injury can often be made during the operation, especially by careful inspection of the wound bed before peritonealization. In this manner he discovered such an injury in 7 of the 10 cases which he reports. Escape of urine from the vagina or the abdominal incision or complaint of incontinence following pelvic operations should always suggest the possibility of ureteral fistula, and should be investigated by cystoscopy when the patient's condition permits. Theoretically, this accident should be entirely preventable; in practice, however, it cannot be entirely eliminated. This is particularly true when there are congenital anomalies of the ureter, or when the ureter passes directly through tumor tissue. If the anatomy of the cervix and its neighboring structures is normal, the ureter lies 1.5 cm. from the uterus at the level of the internal os, and 1 cm. from the cervix at the vaginal reflection. These distances are increased when the bladder is dissected off the anterior wall and retracted downward and forward, while upward traction is made on the uterus. Therefore, if the dissection and retraction are properly done, and clamps or sutures are placed as close as possible to the uterus, the safety of the ureter can be guaranteed. In the presence of complicating conditions the most effective protection for the ureter lies in its exposure throughout its entire course through the parametrium. No attempt to remove the parametrial tissue should be made until this precaution has been observed. The introduction of

ureteral catheters preliminary to total hysterectomy may be of great value, although it is occasionally impossible to palpate the ureter even with the catheter *in situ*. Prevention of ureteral injury during vaginal hysterectomy depends first, upon the proper selection of cases, with elimination particularly of intraligamentous fibroids; second, upon making strong downward traction on the cervix while the bladder is dissected off the anterior wall of the uterus and by subsequent retraction of the bladder anteriorly; and third, by placing parametrial sutures as close as possible to the uterus. By observing these precautions he has not injured the ureter in a large number of vaginal hysterectomies. During the removal of intraligamentous cysts, the ureter may be safeguarded by blunt dissection of the tumor from its bed; in no case should adherent strands of tissue be cut until their nature has been determined. With fibroids developing within the cervix, danger may be avoided by splitting the uterus from the fundus downward and enucleating the tumor, after which the parametria may be clamped and cut as close as possible to the collapsed capsule.

A wide variety of procedures is available for the repair of an injured ureter and proper selection depends upon the type and location of the lesion, the time of discovery and the general condition of the patient. When complete section of the ureter is discovered before closing the abdomen, the most successful repair consists in implantation of the proximal end into the bladder. He has done this five times with primary healing in all. In high injuries, vesical implantation may be impossible and in such cases end-to-end anastomosis over a large catheter appears most promising but should always be accompanied by drainage of the kidney pelvis through a pyelostomy or ureterostomy above the line of repair. Should the condition of the patient be so alarming as to prohibit attempts to repair the injury, the proximal end may be doubled upon itself and ligated with a non-absorbable ligature, or it may be carried out through the incision or into the vagina, thus creating a fistula to be treated later.

Incomplete section of the ureter may be repaired by simply closing the defect, providing that no more than one-third of the wall is involved. If the damage is more extensive, the section should be completed and the proximal end implanted into the bladder. Bilateral ligation of the ureters should be treated by immediate laparotomy with removal of the ligatures if the patient's general condition will permit, otherwise bilateral pyelostomy must be performed with the hope that the ureters may be restored when operation can be tolerated. Postoperative ureterovaginal fistula should be treated expectantly for a time, since spontaneous healing occurs occasionally. If drainage continues for more than 6 weeks, one should attempt to conserve kidney function by transperitoneal implantation of the ureter into the bladder, which is generally preferable to nephrectomy.

In reporting 16 cases of accidental ureteral injury, Stevens[2] states that in 4 cases perforation occurred during cystoscopy, in 5 the ureter was injured during hysterectomy, in 2 during the removal of pelvic cysts, and the other cases during various pelvic operations. The left ureter was injured in 10 cases, the right in 5 cases and both ureters in 1 case. Ten patients recovered, 6 with good kidney function, 3 with probable destruction of the kidney and 1 after nephrectomy. Two

patients died. The 4 cases of perforation recovered, 1 following evacuation of a periureteral abscess, the others without complications. Regarding the treatment of such injuries he states that if a ureter has been completely severed or badly crushed, suture of the proximal segment into the distal or end-to-end anastomosis over a catheter has proven satisfactory. In the latter operation he also advises drainage of the kidney by inserting a ureteral catheter into the ureter through an incision above the anastomosis, and the kidney is drained temporarily through the loin by means of this catheter. Uretero-vesical anastomosis, preferably retroperitoneally, has given some good results, but must be done without tension on the suture line. If anastomosis is not feasible, infection is absent and the opposite kidney is healthy, ligation of the proximal end of the ureter is justifiable, but if the kidney is infected, nephrectomy is indicated when the patient has recovered from the shock of the primary operation. If the function of the opposite kidney is not satisfactory, nephrostomy, ureterostomy or intestinal implantation of the ureter are to be considered. If the ureters have been accidentally ligated and deligation is too hazardous, temporary drainage by means of nephrostomy is usually indicated until the ligature has been absorbed and drainage reëstablished. Deligation is often attended by hemorrhage and is usually difficult, especially if attempted some days after operation.

From Rotterdam comes a report by ten Berge[3] stating that he has implanted ureters into the bladder 4 times and has done an end-to-end anastomosis 3 times, and he found that after the latter operation the kidney function and pelvis remain normal for a longer period of time. In 3 of the 4 implantation cases hydronephrosis and pyelitis developed. The plan which he follows in uniting the cut ends of the ureter is as follows: the proximal portion of the ureter is incised longitudinally a short distance above the cut end and 2 tubular drains are inserted, 1 directed toward the kidney to drain the urine, the other directed toward the bladder. Over this latter drain both cut portions of the ureter are threaded and the ends are sutured together with 3 or 4 fine linen sutures. These drains are then led extraperitoneally to the abdominal wall in the region of the anterior, superior iliac spine. Since the site of the anastomosis is kept dry, there is very little danger of infiltration with later stricture formation. The drains are removed in from 2 to 3 weeks, and the incision in the ureter through which they passed closes itself in a few days.

After a urinary fistula has formed as a result of ureteral injury, if it does not close spontaneously, surgical repair will often be considered, as a patient who is constantly wet with urine is most miserable as well as a social outcast. However, surgical repair of such a fistula, as previously stated, may be quite a hazardous procedure. It is well to remember, as Sears[4] points out, that modern Roentgen ray therapy can destroy normal and diseased kidneys. The intricate epithelial structure of the kidney is replaced by connective tissue. The vascular and glomerular units are the last to be affected. He reports a case of renal fistula which was cured by irradiation and he considers such therapy a safe procedure, provided the treatment is given by an expert roentgenologist.

Ureteral Calculus. When a stone becomes lodged in juxtavesical portion of the ureter the vaginal approach to this portion of the ureter has often been recommended. Kneise[5] objects to the vaginal approach because of the frequent inability to find the stone at the time of operation even though it was palpable before. The relaxation of anesthesia permits the stone to slip up the ureter. In the operation which he advocates, after opening the abdomen through a midline incision, the uterus is pulled out of the wound, the bladder peritoneum is opened and the bladder is pushed well down from the uterus as in the Wertheim operation. The region of the entrance of the ureter into the bladder is slowly and carefully exposed so as not to injure the vessels in the broad ligament. The peritoneum is free laterally and the superior vesical artery is in the field and below it is the ureter. If the stone is palpable it is not necessary to free the ureter from its bed. If the ureter is very thin and presents a hydroureter above the stone, the urine is drawn from the ureter with a syringe so as to minimize peritoneal contamination. Before opening the ureter the patient is placed in the Trendelenburg posture and the surrounding field protected with gauze pads to prevent soiling with urine. While the assistant presses over the ureter proximal to the stone, a small incision is made over the stone and it is gently squeezed out or is extracted with forceps. The ureter is closed with a few fine sutures in the outer coats, the bladder peritoneum is sutured and the wound closed. In this technique it is not necessary to ligate the uterine vessels or sacrifice the adnexa of the affected side as usually described in textbooks. The method is only to be applied in cases where the stone is within 5 cm. of the ureteral orifice. Stones higher in the ureter should be approached by the lumbar extraperitoneal method.

Ureteral Obstruction in Cervical Cancer. When cancer of the cervix advances to the point that there is involvement of the broad ligament, it is only a question of time until the ureter becomes obstructed. In a study of this type of ureteral obstruction Drexler and Howes[6] found that in every case the chief complaint is pain, ranging from a dull ache to a severe colic on the affected side. Usually the patient complains of a constant dull pain located deeply in the groin and referred to the thigh and leg, often simulating an attack of sciatica. It is frequently referred to one or both kidneys, especially when complete occlusion of the ureter has taken place with dilatation of the ureter above the obstruction. The patient often develops a marked distaste for food but with removal of the ureteral obstruction the appetite returns and the gain in weight is rapid, in some instances from 10 to 100 pounds. On physical examination through the rectum a moderate degree of induration, which is tender to touch, can be felt extending laterally. Cystoscopy with ureteral catheterization and pyelography establishes a positive diagnosis and in practically all cases the obstruction will be found in the terminal portion of the ureter. From their autopsy findings they believe that these strictures are the result of pressure on the ureter from invasion of the broad ligament by the malignant process itself and therefore they deem it necessary to direct therapy to this area with the same vigor as the primary lesion in the cervix has been attacked. Up to the present time no satisfactory radiation therapy has been devised for the broad ligament, although many methods have

been devised. Their most satisfactory results were obtained not from irradiation but from ureteral dilatation. The ureters were dilated about every 14 days with the instillation of 1% silver nitrate solution into the kidney pelvis. In many cases catheterization was at first difficult but filiform bougies were eventually passed by the point of obstruction. These were allowed to remain *in situ* for 48 hours and then followed by larger bougies or catheters. In the presence of infection, especially with marked elevation of temperature and a large amount of infected residual urine in the kidney pelvis, the catheters were allowed to remain *in situ* for several days. Occasionally nephrectomy was necessary. Although they have transplanted the ureters into the sigmoid in 2 cases, they feel that this procedure is too hazardous. Implantation of the ureters into the loin causes little shock and is technically much simpler to carry out and should be done where ureteral dilatation has failed.

Bladder Fistulas. In reporting 17 consecutive successful closures of bladder fistulas, Schmitz[7] states that certain points in the preparation of any case are very important. All ulcerated areas in the genital canal must be healed before any operative procedure is attempted, calcareous deposits should be removed as nearly as possible and bladder infection reduced to a minimum. Before operation the opening in the bladder must be accurately located by cystoscopy and its relation to the ureters and the patency of these structures must be ascertained. He advises against freshening the edges of the defect. In most textbooks dealing with fistulas, the suggestion is made that after the tract is freed the hard, firm edges of the opening should be carefully cut away. He warns against cutting anything away because all the tissue is needed in the repair and he considers it important to sacrifice nothing. The edges should be freed and turned in and the raw surfaces brought together as near the free margin as possible. By saving all tissue, if a failure should result, the opening will not be any larger than the original defect. It is important to make a free and wide dissection of all possible surrounding tissue. No suture will hold in soft tissue under tension and the only way to avoid tension is to mobilize structures. There must be sufficient bladder wall available not only to allow a closure of the opening but also to permit the placing of one or two rows of supporting sutures. To accomplish this requires a willingness to free tissues in all directions. The manner of placing sutures is important in two ways. A pucker should never be caused. If tissue buckles, surface adaptation is interfered with and the results are jeopardized. If working near the ureters one should place the sutures so that they follow the long axis of the tube and not across it. A non-absorbable suture should never be used in the bladder. If the catgut does not hold it is almost surely a fault in the operative technique and not the suture material which should carry the blame. Another important point in suturing these wounds is the obliteration of all dead spaces. One must suture the deeper to the more superficial structures, or pockets will develop which may undo the best operative procedure. After the fistula has been closed an iodoform pack is placed in the vagina along the suture line in order to prevent oozing and to aid in holding the raw surfaces to one another. It also reduces the bacterial flora to a minimum during the early postoperative period but should be removed at the end of 24 hours. A catheter is always introduced into the bladder at the end

of the operation and fixed there and allowed to remain for at least a week. Posture is very important in the after-care of these patients. One must try to drain away as much urine from the suture line as possible, not merely to keep the incision dry but to prevent even the slightest pressure upon the repaired area. If there is only a tiny bit of constant fluid pressure, seepage may occur. To obviate this, one should make the most dependent portion of the bladder that area farthest away from the suture line. In other words, in all posterior fistulas, and this means practically all of them, the patient should be placed flat on the abdomen with the head of the bed slightly elevated. This position must be maintained for at least 5 days, no matter how uncomfortable the patient may be. After this a little lying on the side and gradual turning to the back is allowed. The nursing care of these patients must be perfect. The drip of the catheter must be under constant observation so that no possible backing up of urine can occur as the result of blockage. The catheter itself is run down between the patient's legs and out at the foot of the bed, never over the side, so that the urine will fall gradually to the bottle by gravity and not be forced to flow over even a slight elevation. The tube is protected by sandbags so that the legs have no chance to compress the lumen, and it is irrigated once or twice daily with boric acid solution. While it may seem that we have gone into quite some detail in presenting the work of Schmitz, it is only by paying strict attention to such details that a satisfactory result may be expected in many of these cases, as those who have tried to repair extensive fistulas have found out for themselves.

At the Mayo Clinic, according to Stephenson and Masson,[8] these cases are repaired by a modification of the method proposed by C. H. Mayo. After a thread is passed through the fistula at cystoscopic examination, a silver wire is drawn through the tract to act as a guide. The vagina is incised in a transverse direction on each side of a circular cut about the fistula and the base of the bladder is separated from the anterior vaginal wall. With the wire as a guide, dissection is carried well up toward the mucosa of the bladder and a purse-string suture of 00 chromic catgut is placed in the muscular layer. The greater part of the fistulous tract is excised and the vaginal end of the wire is grasped in a blunt hemostat. By making traction on the other end of the wire, the stub of the fistula is inverted into the bladder and the purse string is pulled tight. Reinforcing sutures of catgut are placed in the longitudinal axis and the transverse cut in the vaginal wall is closed separately, using interrupted sutures of silkworm gut. When the two lines of suture can be separated by normal tissue, the chances of permanent closure are good. A retention catheter is left in the bladder for about 10 days. In a few cases in which the vaginal approach is impracticable, either because of the position of the fistula or because the vaginal orifice is so small, it may be advisable to use a transvesical approach. The above description of the operation makes it seem so simple that one might expect uniformly satisfactory results, but such is far from the truth. Repair of the fistula is not effected at the first attempt as a rule, as was seen in the review of cases encountered at the Mayo Clinic. Of 24 cases with vesicovaginal fistulas, the condition of 17 was considered suitable for operation. There had already been

48 attempts at closure on these 17 women. While they were under care at the clinic it was necessary to do 23 operations; 4 of the cases are not entirely cured as yet and the end-result of treatment on 1 other is questionable. Usually if the fistula is 1 cm. or less in diameter, good results can be expected. However, the prognosis of any one attempt is not good if the field in which one is working is mainly scar tissue resulting from previous operations. Sometimes it is impossible to secure sufficient tissue with adequate blood supply to allow closure of the defect, and transplantation of the ureters into the sigmoid becomes necessary. It is probably wise to transplant the ureters in 2 stages, although in selected cases Coffey's second technique, in which both ureters are catheterized and transplanted at the same time is highly satisfactory. The closure of a small fistula by electrocoagulation has been suggested in recent years by European surgeons, but at the Mayo Clinic they have had no experience with the method. They feel, however, that best results with such a method will be secured when the fistula is not more than 1 or 2 mm. in diameter.

Non-purulent Urethritis. This condition, which is also known as granular urethritis and cystalgia, is discussed by Ormond,[9] who states that it is a benign and very common ailment which is often overlooked. He believes that it is a urethrotrigonitis caused primarily by congestion and secondarily by infection. In this condition there are urinary symptoms but no abnormal urinary findings or else very minor ones. The condition is found at all ages after puberty, though most frequently in middle age. The most common symptoms are frequency of urination and dysuria, more marked during the day, while at times there is marked urgency. The treatment of the condition consists of dilatation of the urethra with graduated dilators and the instillation into the bladder of a mild antiseptic such as argyrol or mercurochrome once or twice a week. Occasionally it may be advisable to apply 10% silver nitrate solution to the upper urethra and bladder neck. The urine should be rendered bland and hot sitz baths or douches often give comfort. It should be remembered that recurrences are common, sometimes after many months.

Stricture of the Urethra. Although stricture of the male urethra is recognized as a common ailment, in the female urethra stricture has usually been considered an infrequent condition, and for this reason a careful examination for its presence is seldom made. In discussing this subject Wynne[10] considers any obstruction to the passage of a sound that will pass the meatus as a clinical stricture, except a tumor, stone or other foreign body. Obstructions due to scar tissue, not involving the urethral walls, are not strictures although the symptoms are similar. The measurements made by various investigators show that the normal meatus measures from 18 to 30 F. and the majority is from 23 to 30 F. The finding of so many strictures at the meatus which have been reported by other observers suggests that they consider the "ring" type meatus as a stricture if it is of a caliber less than the average. Wynne is not convinced that a "ring" type meatus should be considered as a stricture even when small unless there is other evidence. It is a simple matter to excise a small wedge of the posterior portion of the meatus for microscopic sections and at the same time effect a cure if the size of the meatus is the cause of the symptoms. In 36 women

he has found an area of narrowing which was apparently abnormal and in those that occurred above the meatus the narrowing was of smaller diameter than the meatus. Gonorrheal urethritis was the most common known etiologic factor, although childbirth caused sufficient injury to the urethra in certain instances for stricture to develop. In nearly half of the series the etiology was not determined. As to location, 24 strictures occurred in the lower third of the urethra; 3 of these were at the meatus and 3 just within the meatus. There were 3 strictures of the middle third, 6 were in the upper third and 3 of these involved the sphincter. There was 1 generalized stricture beginning a few millimeters above the meatus. There were no multiple strictures in the series. The complaints of these patients were numerous, consisting most frequently of burning on urination and frequency and of less importance were complaints of nocturia, urgency, dysuria, hematuria and dribbling. Dilatation of the urethra with Hegar dilators was performed on the average from 4 to 8 times at intervals of from 1 week to 2 months. Thirteen women were observed from 1 to 8 years and were completely relieved when last seen, 8 were improved and 1 was unimproved. Temporary relief was obtained in 3 cases for from 4 months to 1 year, while the remaining cases in the series have not been followed sufficiently to report. Wynne does not believe that stricture of the female urethra is by any means a common ailment but it is a distinct entity which will usually respond to proper treatment.

Carcinoma of the Urethra. There have appeared in the literature reports of 149 authentic cases of carcinoma of the female urethra, but the case reported by Menville and Counseller[11] is apparently the first case of mucoid carcinoma of the female urethra which has ever been reported. An interesting feature of their case is the appearance of inflammatory tissue in the specimen removed for biopsy. Since carcinoma of the female urethra grows slowly and produces symptoms relatively late, it is practically impossible to detect a lesion in its early stages. The symptoms and signs are not typical even in the late stages of the disease, therefore the only reliable method of diagnosis is biopsy. Yet, in this case it has been shown that it is possible to arrive at an incorrect diagnosis even with biopsy. The dense infiltration of inflammatory tissue along the periphery of the urethral growth offers a satisfactory explanation for the inflammatory tissue in the specimen. It is interesting to note that the sensation produced by the urethral mass in this case was similar to that produced by a prolapsed uterus which had been present 38 years previously. Of significance is the fact that for 15 years difficulty in voiding was, with the exception of one attack of acute retention, and the presence of the mass between the labia, the only symptom referable to the urethral growth. It was also noted that an unusual type of urethral caruncle was present 14 years previous to its ultimate removal, while the absence of induration around the urethra was another interesting fact. It has been estimated that the average age at which carcinomas of the female urethra are seen is 53.4 years. The lesions are either in the external part of the urethra or involve all of it. Rarely are they in the posterior part of the urethra. These tumors are of slow growth and not infrequently the first symptom or sign noted is a metastatic nodule in the inguinal nodes. The most frequent symptoms and signs are difficulty in voiding or reten-

tion of urine, hematuria, tumor or metastasis, pain or dysuria, frequency and a discharge from the meatus. The most common finding is a non-pedunculated, indurated growth. In addition there may be tenderness, ulceration and a tendency to bleed. The lymphatic vessels of the female urethra drain into the external iliac, hypogastric and sacral nodes. Results of treatment, regardless of the method used, are highly unsatisfactory. Good results in some cases have been reported following surgical procedures, irradiation, or both. The best prognosis is offered in cases in which the lesion is localized in the anterior part of the urethra, where it can be totally removed by surgical measures.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF
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THE TREATMENT OF SYPHILIS BY INDUCED FEVER.

APPLICABILITY, CURRENT METHODS, RESULTS.

Introduction. The treatment of various stages of syphilis by induced fever has progressed rapidly with a series of important transitions during the past half decade. Mortality, the first consideration, has fallen rapidly with the establishment of a technique. A series of figures collected by Stokes and Pillsbury[1] for malarial therapy up to

1933 showed a range from zero to 32%, with an average of 12.7% deaths. Since the principal groups in this tabulation were collected, the rates of experienced American malarial therapists quoted as 0.5% (Cole),[1] 1% (O'Leary),[1] 2% (Osborne),[1] have fallen to even lower figures, such as O'Leary and Welsh's[2] last-quoted estimate of 0.57% in the final 200 cases, as compared with 5% in the first 100 treated. Jones and Spencer[3] have reported a series of 47 cases with no deaths. On the other hand, a very recent report by Karnosh and Williams,[4] in a series of 580 patients, returns the mortality practically to the average of previous years, namely, 12.7%. In the estimation of mortality from fever therapy procedures, a personal equation inevitably enters into interpretation, and the figures are markedly affected by the character of the material, which, of course, is much more favorable in youthful patients in the early stages of neurosyphilitic involvement than it is in late and degenerative material of public institutions. It is clear, however, that two things materially affect the mortality of fever therapeutic procedures. The first is the experience of the therapist, and the second is the development of special facilities for the work. The very great importance attached to these two desiderata is borne out in practically every society discussion of fever therapeutic problems. Since malaria remains the least controllable and the most beset by complications of any of the fever therapeutic methods, its mortality figures may be accepted as representative of the greatest rather than the least risk which the patient is asked to assume when his infection is treated by non-specific procedures. With the fall in mortality conditioned by greater experience of fever therapeutic methods, there has come a notable extension of the field of usefulness. Within the past several years, the procedure, at first confined to the treatment of paretic neurosyphilis, has been extended to asymptomatic neurosyphilis, to early syphilis with prophylactic intent, to prenatal syphilis, especially when complicated by interstitial keratitis and obstinate osseous lesions; to malignant precocious tertiarism in syphilis, to refractory osseous lesions in general, to serologic fastness and even to the treatment of the chancre (Kyrle).[5] This enthusiasm, while understandable, is not always commendable. It should be clearly understood that the justification for employing a non-specific method in a stage of syphilis such as the primary lesion, in which specific methods of known high effectiveness already exist, is experimental, and experimental in the direction of increasing inaccessibility and difficulty rather than increasing simplification and availability. The emphasis on central facilities, individual experience, complicated technique and especially trained assistants alone, for the time being at least, raises insuperable objections to the attempt to popularize fever therapy for the general treatment of the earliest stages of syphilis.

The notable tendency toward simplification, together with the falling mortality of fever therapy procedures, will, however, in the future, probably render them increasingly available as adjunct treatment for refractory aspects of the disease in the above mentioned fields. Simplification is taking place primarily through the elimination of electrical agents for the induction of fever and by the increasing usefulness and safety of certain types of non-specific protein therapy, notably with the H fraction of typhoid antigen.

Classification of Methods. A very useful classification of current methods of fever therapy is provided by Tobias,[6] which is quoted as follows:

1. Inoculation with infectious disease: (*a*) Malaria (tertian); (*b*) recurrent (relapsing) fever; (*c*) sodoku (rat-bite fever).
2. Injection of avirulent bacteria and their products: (*a*) Tuberculin; (*b*) typhoid vaccine and its fractions; (*c*) gonococcus vaccine; (*d*) dmelcos (Bacillus ducrey) vaccine; (*e*) saprophytic vaccine (neosaprovitan B).
3. Injection of non-specific chemical and biologic products: (*a*) Sodium nucleinate; (*b*) milk; (*c*) peptone; (*d*) turpentine; (*e*) sulphur (sulphur in oil, or sulfosin); (*f*) blood (autohemotherapy).
4. Physical measures: (*a*) Hot baths; (*b*) diathermy (high-frequency); (*c*) short wave (radiothermy or oscillothermy); (*d*) infrared radiation (hyperpyrexator); (*e*) hot air or conditioned air cabinets (hypertherm); (*f*) blankets and externally applied heat (hot-water bags, etc.).

Among these methods, relapsing fever, rat-bite fever, sodium nucleinate, turpentine and sulphur in oil can be rated as on the decline or definitely unsafe; at least so far as American practice is concerned, they may be regarded as retired, notwithstanding occasional favorable reports such as that of Beckman[7] on sulphur.

Within the past 3 years there has been a notable development in the popularity and usefulness of typhoid inoculation, made possible first by the discovery of Nelson,[8] that division of the total dose into two successive injections produces a much more delayed attainment of the always annoying immunity to the bacterial proteins. The fractionating of the typhoid organisms into the "M" and "H" portions, with the demonstration of satisfactory reactivity with minimum complications from the use of the H antigen has placed this technique of fever therapy on a much more satisfactory basis. The demonstration by Simpson[9] and Epstein,[10] that heated air alone in the first instance, and external applications of easily controlled heat by the hot (electric) blanket, could produce satisfactory temperature rises and gratifying therapeutic results, has been a long and important step toward simplification and safety.

None the less, even with the elimination of electrical current passing through the body, and the awkwardness and inconvenience of water baths and the comparative comfort for the patient produced by proper attention to his chlorid intake and output and control of his sweating, fever therapy has not yet become either a harmless or a simple procedure. The maintenance of the body temperature even of a comparatively healthy human being at high levels for a number of hours inevitably subjects the functional groups of body organs to stresses which are estimated with difficulty and which may at times lead to embarrassing or disastrous results.

Modus Operandi. The argument as to the relative importance of histiocytosis, phagocytosis and temperature rise as a spirocheticide and immunity reaction producer still continues, and has made little headway toward settlement as yet. Since Nonnenbruch's summary of the 16 possible modes of action of a non-specific or fever-producing agent in the treatment of disease (summarized by Stokes and Kulchar),[1]

Neyman and Osborne[11] and Bierman and Fishberg[12] have made contributions to the physiologic reactions of the human body under pyretotherapy. The particularly extended study by the latter authors showed increases in the activity of the cooling mechanism, including rising skin surface temperature and increased sweat output, the surface temperature being lower than that in the interior of the body (short-wave radiation therapy). Increases as high as 400% in the velocity of blood flow were observed, and the average increase of pulse rate was 8.5 beats per minute for each degree of Fahrenheit temperature elevation. Systolic blood pressure usually shows a slight elevation followed by a gradual fall to a point below the original level. A free intake of fluid, when allowed, maintains the weight at approximately the pre-treatment level and maintains the blood volume and blood viscosity. Apneic periods were observed in the respiratory rhythm, and the pH of the blood increases. Leukocytes show an initial fall of 25% to 30%, followed by a leukocytosis amounting to approximately 80% above the initial figure, with a great increase in the staff neutrophils and the appearance of immature forms indicating a stimulation of the bone marrow. The leukocytic response declines with repeated stimulation. A high sedimentation rate tends to fall as the temperature rises. Bierman and Fishberg,[12] as a result of their studies, emphasized the importance of the elimination of lactic acid through the sweat in the maintenance of the fever-treated body in acid-base equilibrium. Patients under fever therapy may reach an extreme degree of alkalosis, the pH of the blood reaching levels as high as 7.6. The enormous loss of chlorid through the sweat results in a chlorid-poor urine and a practically total cessation of the secretion of free hydrochloric acid in the stomach. A great increase in hemoglobin in response to the heightened oxygen demand of the patient in fever was observed. The authors mentioned very briefly and without emphasis the thermolethal effect of fever on bacteria; they point out that there is a reduction in the complement-fixing titer of the serum of individuals suffering with gonorrhea under fever therapy, and that similar reduction in the complement-fixing antibody of variously immunized rabbits has also been noticed. Neyman and Osborne[11] pointed out the slowness of the rise of temperature under externally applied heat, and state that the atmosphere surrounding the skin should not be allowed to rise in temperature above 130° F. unless the air is kept in constant motion by means of a blower or turbine. Blanket temperatures above 120° F. are regarded by them as dangerous. The deep body temperature is some 2 degrees higher than the subcutaneous temperatures of the thorax and abdomen. The authors believe that it should be possible to maintain the temperature of 42° C. for 1 hour, or 41° C. for two hours, within the body, which is necessary to destroy the Spirochæta pallida. In their discussion of the physiologic reactions to various therapeutic techniques, these authors state that cyanosis, the beginning failure of the respiratory apparatus, and a great tendency toward heat prostration is noticed in the more exhausting blanket treatment, as contrasted with the diathermic or radiothermic therapy.

Malarial Therapy. While malaria was originally introduced for the treatment of parenchymatous neurosyphilis, particularly paresis, there is a growing tendency to enlarge the scope of its usefulness. Freeman[13]

believes that those types of neurosyphilis which show minimal clinical signs in association with positive serologic reactions respond best to therapeutic malaria, and the author has seen the highest percentage of good results with asymptomatic neurosyphilis, paresis sine paresi, early dementia paralytica, early tabes and basilar meningitis. He is not enthusiastic for the results obtained in late tabes, advanced dementia paralytica, optic atrophy, nerve deafness, vascular occlusions and congenital neurosyphilis. O'Leary[14] believes that asymptomatic neurosyphilis, which is to be anticipated in about one-fifth of all cases of the disease, and in which an adequate defense mechanism is apparently lacking against subsequent parenchymatous involvement, responds particularly favorably to the influence of malarial therapy, which is able to prevent parenchymatous neurosyphilis from developing in at least 50% of the patients. Ambler and Van Cleve[15] are enthusiastic about the results obtained with malarial therapy in syphilitic interstitial keratitis. In the past 6 years the authors have treated 17 patients with inoculations of malaria with uniformly excellent results. Corneal opacities seem to be more completely and rapidly absorbed than with any other type of therapy, and no better results were obtained in patients who had had previous antisyphilitic treatment than in those who had had none. Recurrences were noted in 2 cases, occurring a few weeks after the inoculation of malaria, and responded well to the usual antisyphilitic treatment. In 5 patients, one eye only was involved when malarial treatment was begun, and the second eye did not become involved in any of them. There were no fatalities.

O'Leary and Welsh[2] report the experience of the senior author in the treatment of nearly 1000 patients with malaria over a period of 9 years. Stress is laid on certain disadvantages of treatment with malaria which have prevented the method from becoming used as a routine in cases of neurosyphilis. In 10% of the patients inoculated it was impossible to induce chills and fever, owing to an immunity to the infection. The therapeutic use of fever is contraindicated in the case of a debilitated syphilitic patient or in the presence of advanced disease in any of the vital viscera. While the original mortality rate was high, the authors now believe that death from treatment by malaria should occur rarely and only as the result of some accident. In the past 4 years of the authors' experience, the mortality rate has fallen to 0.57%. Occasionally a patient with dementia paralytica is made worse by treatment, in the authors' series the clinical symptoms being accentuated in 2.2% of the cases in which dementia paralytica, according to clinical evidence, was present. Of the 186 cases in which the clinical signs of advanced dementia paralytica were sufficient to warrant hospital care, a complete remission developed in 35%, and an additional 35% of patients were sufficiently benefited to be permitted to go to their homes. In 42% of the cases in which the spinal fluid was reëxamined recently, the test was found to be reversed and completely negative in all respects. The authors expressed it as their observation that in more than three-fourths of the cases of asymptomatic dementia paralytica the clinical progress of the disease was arrested. Following treatment, the serologic tests of spinal fluid became reversed to complete negativity in almost half of the cases of asymptomatic neurosyphilis, in which routine measures had previously failed to have a favorable

influence on serologic characteristics. The results in the treatment of the tabetic forms of dementia paralytica and tabes dorsalis were likewise favorable in about half the cases, whereas among serologically negative tabetic patients with resistant complications, the crises and pains in the legs were only slightly benefited. Solomon[16] has observed 174 patients following malarial therapy and confirms the figures of O'Leary in reporting that 65 (37.3%) were sufficiently improved to be able to resume work, while 22 (12.6%) were improved but not self-supporting. This means that about half of the patients were so improved that they were able to live in a normal community. Solomon believes that the amount of subsequent treatment and time play an important part in the serologic results. There is no complete parallelism between clinical and serologic results, and a negative reaction to tests of the spinal fluid is necessary before treatment can be discontinued. MacDowell[17] believes that a gain in weight following malarial therapy has considerable prognostic significance, the more gradual the gain the more favorable and lasting the result. The author believes that the benefits derived from therapeutic malaria are of a practical nature, inasmuch as the patients who improve are able to engage in useful pursuits about the hospital even when not sufficiently recovered to be discharged and become self-supporting. Those who die, on the other hand, are spared a lingering death and gradual destruction of body and mind, and are usually in bed only a few weeks instead of months which was formerly the course which these cases pursued. Holzer,[18] in 280 cases in which malarial treatment was advisable, found contraindications existing in 28%. These included trauma and operations on the skull, epilepsy, alcoholism, psychoses, heart disease, pulmonary, renal and other severe organic diseases. These figures indicate the need for critical selection before malarial treatment is instituted.

Foreign Proteins. The dangers and limitations attending the use of malaria have stimulated interest in the past few years in other means of producing hyperpyrexia. Typhoid vaccine has been recognized for some time as a safe and convenient method of inducing fever, as indicated by the work of O'Leary,[19] Kemp and Stokes[20] and others, but the difficulty of producing a sufficiently high fever comparable to that of malaria has been a serious drawback to its more general adoption. This has been largely overcome, however, by the suggestion of Nelson,[8] that a second injection of vaccine, given at the height of the fever produced by the first, is capable of inducing fever sufficiently high to be of therapeutic value. Recently Driver and Shaw[21] have studied 19 patients with neurosyphilis and 2 with resistant syphilis associated with interstitial keratitis and iritis by the divided method of Nelson.

The technique advised by the authors is as follows: Fresh commercial typhoid vaccine was used, containing 1 billion organisms per cc. One cc. of the vaccine is added to 9 cc. of physiologic solution of sodium chlorid. One cc. of this mixture contains 100 million killed organisms. If a fresh vaccine is used, smaller doses are required. As a general rule, treatment is given on alternate days, although it can be given on successive days, providing the temperature has returned to normal, the reactions are well sustained and there are no other contraindications. Temperatures are taken rectally every half hour until the temperature

has risen to 104° F., and then every 15 minutes until it falls to 104° F. again. Thereafter the temperature is recorded hourly until normal. It is advisable to avoid the use of antipyretics for the relief of headache and other symptoms during the course of the treatment, as they may greatly diminish the fever reaction.

The first dose is given at any convenient time, preferably in the morning, followed by a second dose after the temperature has reached 100° F. or above. The interval between doses should not be less than 2 hours, and an interval of 3 to 6 hours is entirely satisfactory, providing the temperature has not dropped back to normal by that time. A course of treatment may consist of any number of reactions. As many as 10 to 16 have been given. Subsequent courses may be given to a patient with an equally satisfactory result after an interval of weeks or months. The initial dose of the vaccine rarely exceeds 10 to 15 million organisms. The authors believe that the method is an excellent substitute for malaria treatment and brings satisfactory fever therapy within the reach of a still larger group of patients suffering from neurosyphilis. Several courses of treatment can be given without the establishment of a permanent immunity and chemotherapy can be combined with it if desired. Higher temperatures made possible by this method clearly demonstrate the advantage obtained over the older method of inducing fever by the injection of typhoid vaccine.

Recently attention has been focused on the typhoid "H" antigen vaccine for debilitated patients who cannot stand the severe systemic reactions produced by whole typhoid vaccine. Schnitker[22] has treated 25 patients with dementia paralytica physically unsuitable for treatment with malaria, full typhoid vaccine, or diathermy with typhoid "H" antigen (flagellar) alone and in combination with tryparasamid, and believes that the systematic serologic improvement obtained by this method compares favorably with the results secured with other forms of fever therapy. It has the following advantages: (*a*) Although the hyperpyrexia equals that obtained with full typhoid vaccine, the concomitant illness is far less severe. (*b*) It does not involve superimposing a second and perhaps lethal infection on an already existing one, as with malaria. (*c*) It does not involve the risk of burns and renal damage, as with diathermy. (*d*) The contraindications are but four, namely: (1) Severe cardiorenal disease; (2) active pulmonary disease; (3) severe cachexia; (4) acute infections with a rapid sedimentation rate.

Furthermore, the administration and control of this method of treatment is simple, and may be adopted by the general practitioner, both at the hospital and in the home. In the experience of the author, it has not been associated with complications or sequelæ. The injections are given 3 times a week, intravenously, the initial dose used being 50 million organisms (killed bacilli equivalent). H antigen builds up a partial immunity as does whole vaccine, and increasing doses must be given at subsequent injections. The dose at the second injection is usually 200 million organisms, and after the third, 400 million, the number advancing 200 million per time up to the sixth injection (1 billion organisms). After this it is found better to increase the dose by 400 million organisms. Doses as high as 8 billion organisms have been

given. Patients who develop an immunity to the vaccine or who were initially immune because of antecedent typhoid were given paratyphoid A antigen H with good results.

Electrical and Other Physical Methods. During the past 6 years the increasing recognition of the fact that the common denominator of all methods was fever production, is largely, if not entirely, responsible for the striking clinical results which have been obtained by the use of the electrical methods of fever production. Neyman and Osborne,[11] King and Cocke,[23] Schamberg and Butterworth[24] and others have shown that diathermy in the treatment of paresis produces results comparable to that obtainable by malaria and other measures. Freeman, Fong and Rosenberg,[25] on the other hand, found diathermy much less effective than malaria. Among 50 patients treated with diathermy no remissions occurred, and while 10 patients improved, subsequent relapse was commonly observed. Since 1931, Simpson, Kislig and Sittler[9] have been engaged in an investigation of the influence of an ultra-high-frequency field on neurosyphilis and other chronic infections. The essential difference between a 1-kw. radio transmitter and the apparatus used for therapeutic fever production is that the energy is concentrated between two large condenser plates instead of being directed from an aërial. The term "radiotherm" has been applied to this altered radio transmitter. The heating effect is produced by a vacuum tube oscillator, composed of two 500-watt radiotrons, producing a high-frequency field of approximately 10 million cycles per second (30-m. waves) between the condenser plates. The radiotherm differs from the diatherm used for fever production in that it operates at a frequency approximately 10 times as great. The spark gaps of diathermy produce damped waves, while the vacuum tube oscillator of radiothermy produces an even flow of continuous waves. In fever production by diathermy, alternating currents of high frequency pass between two large electrodes applied directly to the skin surfaces of the anterior chest wall, abdomen and back. If the electrodes are not maintained in direct contact with the skin surface, arcing occurs, resulting in skin burns.

In fever production by radiothermy the patient merely lies on a stretcher between the condenser plates; no electrodes are applied to the skin surface. However, short radio waves are concentrated in the drops of sweat which accumulate on the skin surface, occasionally producing arcing and burning, and consequently it became necessary to devise some means of allowing the patient to rest comfortably in an insulated air-conditioned cabinet ("Kettering hypertherm"). This has now been accomplished, and by passing a column of heated air over and under the patient it is possible to dissipate the sweat as it reaches the skin surface. Ordinarily it requires from 30 to 60 minutes to raise the rectal temperature from the normal level to the desired height (105° to 106° F.). Temperature, pulse and respiratory rate are recorded before the treatment is begun and every 10 to 20 minutes during the course of treatment, and a high degree of individualization is necessary because of the lack of uniformity in response to fever production by high-frequency methods. While formerly it was the custom of the authors to remove the patient from the cabinet as soon

as the desired temperature was obtained, subsequently maintaining the temperature by the use of heated blankets and flexible rubber electric pads, it is at present found advantageous to the patient's comfort to allow him to remain in the air-conditioned cabinet throughout the entire 5-hour febrile period. Simpson and his co-workers observe the following contraindications for the employment of sustained artificial fever: advanced age, myocardial or renal insufficiency, active tuberculosis, aortic aneurysm, or rapidly progressive late neurosyphilis. The sense of exhaustion commonly experienced by many patients can largely be overcome by supplying large quantities of chlorid-containing fluids both during and immediately after treatment, and the institution of the chlorid-replacement regimen has materially cut the time during which the patient has to remain in the hospital following the return of the temperature to the normal level. In 36 patients with some form of neurosyphilis the authors found that their results compared favorably with those obtained with other non-specific measures. While sufficient time or experience does not as yet permit a full evaluation of such treatment, the practical difficulties and the expense of the equipment involved, necessarily restricting its use to centers of investigation, it is probable that radiothermy represents a distinct advance in the pyretotherapy of neurosyphilis, and when reduced to a more available status may eliminate some of the more dangerous methods now in use.

In a more recent article by Simpson,[26] the results of treatment of 117 syphilitic patients are recorded. The course of treatment was completed on 87 of the group. The best results were obtained by combining specific therapy with at least 50 hours of sustained fever at approximately 106° F. Fever treatments were usually given weekly for 10 weeks, with 5 hours of sustained fever at each treatment. The antisyphilitic drug was injected ½ hour before each fever treatment. After completion of the course, specific chemotherapy was employed at weekly intervals for 20 weeks. On 16 patients with dementia paralytica, 12 obtained complete clinical remission, 2 improved greatly, 2 showed moderate improvement and 1 demented patient was not improved. The spinal fluid reactions to the Wassermann and Kahn tests were reversed to negative in 6 cases. The blood serologic reactions were reversed to negative in 8. Among a group of 7 patients with taboparesis, subsidence of root pains occurred in all. Two experienced recurrence of the pain, but this was controlled by further treatment. In 4 of 5 patients with ataxia the gait improved, 1 being restored to a normal gait. In 9 patients with tabes dorsalis, root pains, in the form of crises or lancinating pains, were abolished in all. In 1 patient the symptoms of cord bladder were overcome. The spinal fluid reactions were reversed to negative in 2, became less positive in 3 and remained positive in 4, while the blood reactions to the Wassermann and Kahn tests were reversed to negative in 4 instances, became less positive in 3 and remained positive in 2.

Epstein and Cohen[10] report a simple method of producing hyperpyrexia by carefully wrapping the patient in blankets and rubber sheeting. Oral temperatures of 104° to 105.8° F. may be produced and maintained for 6 hours by this means. The advantages are that it is cheap, there is no danger of electrical burns and it is less exhausting to the patient

than diathermy or the cabinet. Furthermore, it is easily transported, thus making it available to patients in private wards of general hospitals. Wilgus and Kuhns[27] also are enthusiastic for the use of the electric blanket. They report the results obtained among 500 patients treated with 5 different forms of fever therapy at the Elgin State Hospital and the State of Illinois Psychopathic Institute as follows: Typhoid vaccine: improved, 52%; unimproved, 28%; worse, 20%. Sulphur in oil: improved, 58%; unimproved, 21%; worse, 21%. Malaria: improved, 66%; unimproved, 20%; worse, 14%. Diathermy: improved, 72%; unimproved, 11%; worse, 17%. Electric blanket: improved, 78%; unimproved, 15%; worse, 7%.

Wagner-Jauregg,[28] the father of malarial therapy, cautions against accepting various electrical methods for fever production with too much enthusiasm, inasmuch as so little is at present known regarding the permanency of remissions obtained by these measures. He is, indeed, inclined to doubt whether they will be permanent, because treatment with the radiotherm in his experience had little effect on spinal fluid reactions. He believes that treatment with radiotherm may prove particularly valuable in the treatment of late tabes with positive spinal fluid and may prevent the development of general paralysis. The method does have some advantages over malaria, however, in his opinion, namely, the absence of danger of the transmission of other diseases and the shorter interval of hospitalization involved. Furthermore, the height of the temperature can be controlled and treatment can be distributed over a longer period of time than is possible with malaria. The costly apparatus, however, and a trained personnel do not at present make the method as practical as malarial therapy.

It is apparent from the above summary of recent literature that induced fever has unquestionably established itself as a valuable and, indeed, at times, indispensable aid in the treatment of certain phases of syphilis. While the choice of method is still unsettled and each seems to possess certain disadvantages to counterbalance its merits, continued research in this field will undoubtedly give us a safe, practical and relatively inexpensive method of producing hyperpyrexia.

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(Titles have been omitted for sake of brevity.)

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